Asthma Epidemiology and Environmental Factors in Hong Kong

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Abstract

There has been a rising trend in asthma prevalence in many countries including Hong Kong over the last two decades. The parallel increase in rhinitis and eczema suggests the importance of exposure to allergens and other environmental factors in the pathogenesis of asthma and allergy.

The thesis is divided into two parts - the ISAAC study and residential home survey. In the ISAAC study, the prevalence of asthma and allergy in 4,665 schoolchildren was investigated in different districts throughout the territory in Hong Kong. Using an identical and comparable method including both written questionnaire and video questionnaire, it was found that the prevalence of asthma and allergy in Hong Kong increased in recent years similar to that in other countries. The video questionnaire has been shown to be at least as effective as the ISAAC written questionnaire in predicting bronchial hyperresponsiveness (BHR) in western populations. In this thesis, we validated the video questionnaire in the local Chinese population and found it a simple and valid tool for international comparisons of asthma prevalence and severity. Exposure to the environmental factors in term of major allergens of mite, cat, cockroach, and nitrogen dioxide could be important in the development of asthma and allergic diseases in predisposed subjects in Hong Kong. The home survey aimed to collect baseline data. The distribution of these environmental factors in residential homes in Hong Kong and the findings will form the basis for future comparative studies of indoor environmental factors between populations with contrasting asthma prevalence.

論 文 摘 要

近二十年來， 香港像許多其他的國家一樣， 哮喘的發病率有上昇的趨勢， 過敏性鼻炎和濕疹的發病率也有相應的增長， 顯示出過敏原及其他環境的因素在哮喘和過敏性疾病的病理發生上的重要性。

這篇論文分爲兩部份-- ISAAC (全球性兒童哮喘及過敏性疾病的調查) 的香港數據及香港居民家庭環境的調查。在 ISAAC 中，我們調查了香港不同地區的合共 4,665 個學童的哮喘及過敏疾病的發病率。通過具有統一性及可比較性的書面問卷和錄像帶問卷調查，數據顯示香港跟其他國家一樣，近年來的哮喘及過敏疾病的發病率有所增加。用播錄像帶的方式作爲調查方法，在西方人群中已証實它至少是和書面問卷的方式一樣有效。在東方人群中的調查，我們也証明了這種錄像帶的方法是一種比較不同地區間哮喘發病率及其嚴重性的簡單而有效工具。在香港的易感人群中，暴露於塵 蜱、貓、和蟑螂等致敏原和二氧化氮的環境，是產生哮喘及過敏疾病的重要因素。這次調查香港家庭環境所得的數據爲以後有不同哮喘發病率的人群間的比較提供了基礎。

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Glossary of terms and abbreviations

BHR:	Bronchial hyperresponsiveness
Bla g 2:	major allergen of cockroach
CI:	confidence interval
Der p 1:	major allergen of dust mite
ETS:	Environmental Tobacco Smoke
Fel d 1:	major allergen of cat
FEV_1:	Forced Expiratory Volume in first second
FVC:	Forced Vital Capacity
ISAAC:	International Study of Asthma and Allergies in Children
NO_2:	Nitrogen dioxide
OR:	odds ratio
ppb:	parts per billion
RAST:	radioallergosorbent test
VQ:	Video Questionnaire
WQ:	Written Questionnaire

Chapter 1 Introduction

1.1. Asthma epidemiology

There have been considerable concerns over the increasing trend of prevalence of asthma and allergic diseases in the Western as well as developing countries. Compared with that of the West, the prevalence of asthma in the Hong Kong population is lower but it is noteworthy that both asthma prevalence as well as asthma mortality have been reported to be rising in recent years (Lai 1996A). Similar increasing trends have also been reported in other countries in the Asian Pacific region including Taiwan (Heieh 1992) and Japan (Nishima 1993). Besides, even within the same ethic group, people in different places have different asthma prevalence, e.g. in China, the prevalence was 2 to 3 times less than that of Hong Kong. As a result, a lot of studies have been in these days. Unfortunately, the lack of uniformity of methodology between studies, and the lack of a "gold standard" for defining asthma and allergic diseases make comparison of data between studies difficult. A standardized approach to international and regional comparison of asthma and allergies has therefore become necessary. The international study of asthma and allergies in childhood (ISAAC) was founded in 1989 with the aim to describe the prevalence and severity of asthma, rhinitis and eczema in children in two age groups (6-7, 13-14 years). These children live in different geographical areas so that comparisons could be made between countries; and baseline

measurements for the assessment of future trends in the prevalence in severity of these diseases could be assessed (Asher 1995).

Written questionnaire is the one of most common methods to study asthma prevalence. However, due to different cultures and different languages, misunderstanding may occur. Not surprisingly, a video questionnaire has been developed when a comparison on asthma prevalence among populations of various cultures and languages is made. In ISAAC, both the written and video questionnaires are employed.

The exact reasons for the increase in asthma prevalence in "westernized populations" and the wide variation in prevalence rates among countries in the Asian Pacific region are not entirely known. The rather dramatic worldwide increase in prevalence of asthma as well as other allergic diseases, such as allergic rhinitis and eczema, within a short time-span of 20 years or so favours environmental aetiologies rather than genetic ones. Many proposed environmental factors such as the pathogenic role of allergen exposure, dietary factors, environmental tobacco smoke, childhood chest infections, indoor and outdoor air pollutants have been extensively studied. However, none of the proposed risk factors alone could explain the change in the asthma prevalence on their own.

In Hong Kong, there is limited information on asthma epidemiology. Nevertheless, the available data suggest that Hong Kong has one of the highest prevalence of asthma and allergic disease in South-East Asia when a comparison is made with mainland China and Malaysia (Leung 1994B). In 1995, Hong Kong became a participating center in the Western Pacific region of ISAAC; and the first part of this thesis will report the result of ISAAC in schoolchildren aged 13-14 years. In addition, a comparison with the ISAAC data reported by other countries in the same region will also be discussed. The second part of the thesis focuses on environmental factors that may account for asthma and allergy trend in Hong Kong.

1.2 Aim of study

The aim of this thesis is twofold:

i. To define the prevalence and severity of asthma, allergic rhinitis and eczema in schoolchildren aged 13-14 years in Hong Kong; and to compare the result with that in other countries by utilizing identical methodologies, i.e. written and video questionnaires.

ii. To describe the environmental factors in residential homes in Hong Kong in terms of the distribution of major inhalant allergens of mite, cat, cockroach, and nitrogen dioxide (NO_2). The identification of potential risk factors for asthma and allergy will form the basis for future research on the impact of indoor environmental factors on asthma prevalence in different populations.

Chapter 2 Literature review

2.1 Definitions of Asthma

The word "*asthma*" was derived from the Greek word meaning "*panting*". It has been known and described for more than 2,000 years. Unlike other diseases that have been manifested in ways which are sufficiently distinct from the normal state, asthma has not yet been precisely defined. Therefore, the aetiology of asthma is obscure; the clinical picture is diverse; and there are multiple pathophysiologic mechanisms contributing to chronic airway inflammation, a hallmark of bronchial asthma. It is therefore necessary to decide "what is asthma and what is not," if one is going to claim who or what is being referred to .

For definition purpose, asthma is better thought of as a syndrome rather than a disease. Although Scadding (1983) defined asthma as a "disease" characterized by wide variations of resistance to airflow over short periods of time within intrapulmonary airways, clinicians, physiologists, immunologists and pathologists have expressed different perspectives on asthma.

In clinical and physiological terms, asthma exacerbations are acute or subacute episodes of progressively worsening shortness of breath, cough, wheezing,

chest tightness, or some combinations of these symptoms. Exacerbations are characterized by reduction in expiratory airflow resulting in an obstructive ventilatory defect on spirometry.

With respect to pathophysiological definition, the changes associated with airway obstruction in asthma are thought to be initiated by inflammatory events in the airways. The typical sequelae of airway inflammation include vasodilatation, increased vascular permeability with oedema and exudation of plasma, infiltration of various inflammatory cells, shedding of epithelial cells and mucus hypersecretion (Barnes 1988). In addition, the airways of patients with asthma are infiltrated by inflammatory cells, particularly T-lymphocytes, eosinophils and mast cells. Mast cells are believed to play a central role in the pathogenesis of asthma. There is evidence for an increase in mast cells number in bronchoalveolar lavage of asthmatics, and mast cells from asthmatic patients have a greater "releasability" of containing granules (Flint 1985). These cells interact with one another by ways of various cytokines which can also lead to smooth muscle contraction and hypertrophy. The airway epithelium is often grossly disrupted with desquamation and the mucosa and submucosa become swollen and oedematous as a result of inflammation. Furthermore, ongoing chronic inflammation of the airways leads to thick mucus production which can obstruct the airway lumen. Another hallmark of asthma is bronchial hyperresponsiveness (BHR), a phenomenon manifested by an exaggerated bronchoconstrictive response to a number of physical, chemical and pharmacological agents. Asthmatics often develop symptoms of wheezing and

dyspnea after exposure to stimuli like allergens, environmental irritants, viral infections, cold air, or exercise. Bronchial challenge test using histamine or methacholine has been developed as an objective measure of BHR and its close relationship with respiratory symptoms has been shown previously (Salome 1987). Several investigators have proposed to explain BHR both being an asthma symptom as well as being the primary mechanism for airway inflammation, alterations in autonomic neural control of airways, changes in intrinsic bronchial smooth muscle function and baseline airflow obstruction. Nevertheless, whilst BHR provides an objective measure of asthma, it has been shown to be neither sensitive nor specific to the clinical syndrome of asthma (Josephs 1989, Clifford 1989).Therefore it cannot be relied upon as the sole objective marker for asthma.

From an immunological viewpoint, the airway inflammation in asthmatic airways may be regarded as an aberrant hypersensitivity reaction mediated by IgE. The term *atopy* was coined by Coca in 1922 to describe disease entities such as asthma, hayfever, eczema, and urticaria caused by drugs and foods. Atopic individuals have an innate ability to form specific IgE antibodies to various environmental antigens. This atopic status can easily be demonstrated by skin test using the prick methods as described by Pepys (1975) or by serological testing using radioallergosorbent test (RAST) (Wide 1973). Up to 90% of children and 60% of adults with asthma are atopic and have specific IgE to various environmental allergens (Leung 1997). This type of asthma is sometimes called extrinsic asthma.

The current working clinical definition of asthma recommended by the National Asthma Education Program Expert Panel Report by the National Heart, Lung, and Blood Institute is: "a lung disease with the following characteristics: (1) airway obstruction that is reversible (but not completely so in some patients) either spontaneously or with treatment ; (2) airway inflammation; and (3) increased airway responsiveness to a variety of stimuli (Sheffer 1991)". For epidemiology studies, asthma is difficult to define because an epidemiological definition is not necessarily equivalent to a medical diagnosis. An epidemiological definition can, however, include a medical diagnosis as one component. Two definitions of asthma are commonly used in epidemiological studies: (1) the self-reporting of diagnosed asthma (with or without physician confirmation) or the reporting of certain symptoms suggestive of asthma such as wheeze; and (2) the presence of asthma symptoms (usually wheeze in the past 12 months or current wheeze) plus the presence of BHR (Toelle 1992).

2.2 Questionnaire in asthma epidemiological surveys

Most epidemiological studies of asthma employ written questionnaires to define asthma and related symptoms. These offer several advantages over other methods in ascertaining asthma in large number of subjects, e.g. inhalation and exercise challenge tests. Written questionnaires are widely convenient and acceptable. The first widely used questionnaire in respiratory epidemiology was the questionnaire originated from the Medical Research Council (MRC) of Great Britain.

In the first version in 1960, there were only a few questions about wheezing. In subsequent editions, more questions on asthma and asthma-like symptoms were included and the questionnaire eventually became a powerful tool in asthma epidemiological surveys. Based on the MRC questionnaire, a number of other respiratory questionnaires have been developed and these include the European Community for Coal and Steel Workers (ECSC) questionnaire, and the American Thoracic Society and the Division of Lung Diseases (ATS-DLD-78) questionnaire. In 1984, the International Union Against Tuberculosis and Lung Disease (IUALTD) questionnaire was developed with the intention of using the most valid symptom-based items for identifying asthma (Torén 1993). It was formulated in English and translated into French, German and Finnish. It was subsequently found to give reproducible results in all four languages (Burr 1992).

Although respiratory questionnaires have provided useful estimation of asthma prevalence in the past, they are subjective, faulted with recall biases and can be influenced by a variety of cultural and sociological factors. In the wake of the rising trends of asthma prevalence worldwide, a standardized approach to international and regional comparisons of asthma and associated allergic disease is much needed. For the purpose of comparison within and between countries, an international study of asthma and allergies in childhood was started in 1989 with the express aim to compare the prevalence and severity of asthma, allergic rhinitis and eczema in children in two age groups (6-7, 13-14 years) living in different areas. In an attempt to minimize the difficulties in comparing of information on asthma prevalence between populations with different cultures and languages, a video

questionnaire has been developed. In New Zealand, there were 456 schoolchildren (12.3-19.5 years), in whom English was the primary language, completed a standard written and video questionnaires (Shaw 1992B). The video questionnaire consisted of some short sequences of asthma symptoms in children showing wheezing at rest, wheezing with exercise, and nocturnal wheezing. The video questionnaire was shown on color TV monitors. The participants completed a one page questionnaire during the viewing. The authors concluded that the video questionnaire was more reproducible than the written one. In addition, it has similar sensitivity and specificity with respect to bronchial hyperresponsiveness when compared to standard questionnaires in Caucasian schoolchildren (Shaw 1992A). However, the video questionnaire has not been validated against BHR in the oriental population, and it is one of the objectives of the thesis to test the video questionnaire against BHR in schoolchildren in Hong Kong.

2.3 Asthma Prevalence Studies in Western Populations

Table 1 summarized a number of studies which demonstrated an increase in asthma prevalence by using identical methodologies to study the same age-strata of the populations over time. The rising trend in the prevalence of asthma and allergic disease became immediately apparent in both adults and children. Peat and co-workers found that in Sydney schoolchildren aged 8 to 10 years recent wheeze increased from 10.5% to 14.9% whilst respiratory symptoms including wheeze, exercise wheeze and nocturnal cough increased from 25.5% to 36.8% between 1982 and 1986 (Peat 1990). The same group of investigators also found a similar trend in adults aged 18 to 55 years living in Busselton, Western Australia between 1981 and

Table 1 The increasing trend of asthma prevalence in Western Population

Authors	Years of Study	Methods	Population	Age	Sample Size	Diagnosed asthma %	Current wheeze %
Peat JK	1982	Questionnaire BPT/SPT	Belmont Schoolchildren Australia	8-10	718		10.5
	1984	Questionnaire BPT/SPT	Belmont Schoolchildren Australia	8-10	505		11.8
	1986	Questionnaire BPT/SPT	Belmont Schoolchildren Australia	8-10	380		14.9
William H	1964	Questionnaire	Melbourne Schoolchildren, Australia	7	N/A	19.1%	
Robertson	1990	Questionnaire	Melbourne Schoolchildren, Australia	7	3324	46%	23.1

Table 1 Increased trend of asthma prevalence in Western Population (con'd)

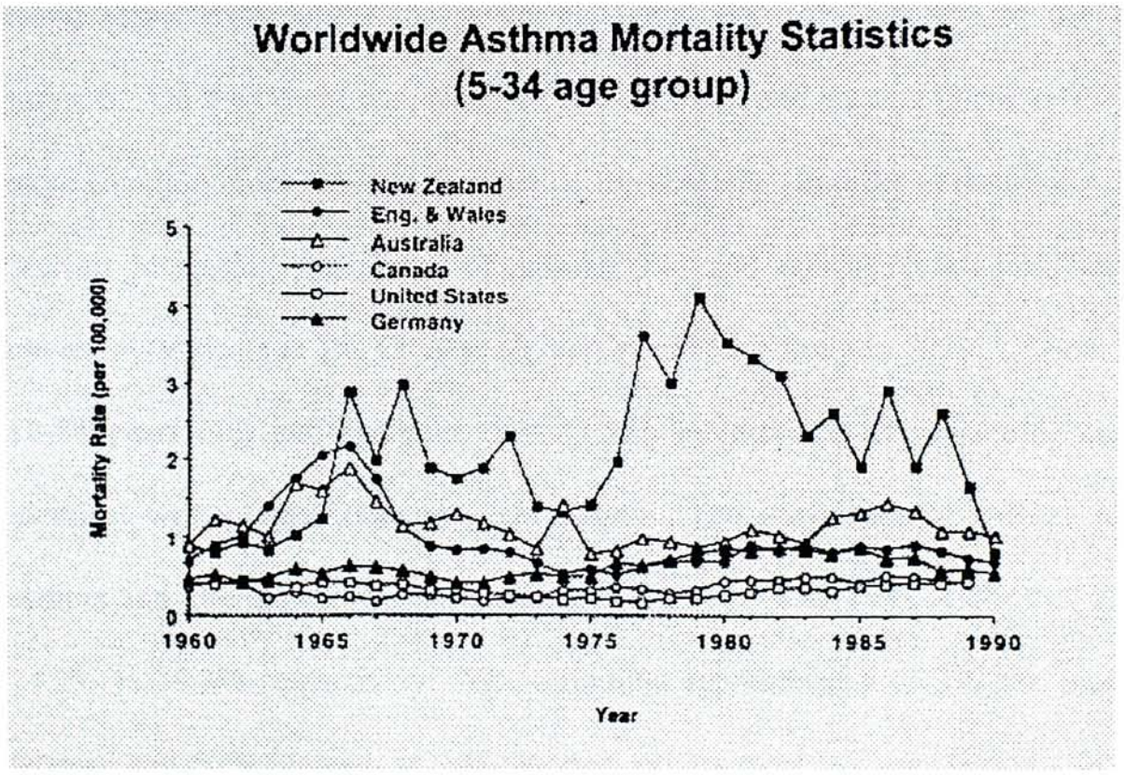
Authors	Years of Study	Methods	Population	Age	Sample Size	Diagnosed asthma %	Current wheeze %
Peat JK	1981	Questionnaire BPT/SPT	Busselton Australia	18-55	553	9.0	17.5
	1990	Questionnaire BPT/SPT	Busselton Australia	18-55	1028	16.3	28.8
Dawson BM	1964	Questionnaire	Aberdeen Schoolchildren Scotland	8-13	2743	4.1	10.4
Ninan TK	1989	Questionnaire	Aberdeen Schoolchildren Scotland	8-13	3942	10.2	19.8
Burr ML	1973	Questionnaire PEFP/EPT	South Wales Schoolchildren Britain	12	817	5.5	4.2

1990 where diagnosis of asthma increased from 9% to 16% and hayfever increased from 21.9% to 46.7% (Peat 1992). In Melbourne, the prevalence of a history of wheeze or asthma among 7 year olds increased from 19.1% in 1964 to 46% in 1990 (Robertson 1991). Similarly, Ninan & Russell showed that, in Aberdeen schoolchildren aged 8 to 13 years, asthma increased from 4.1% to 10.4% whilst hayfever, or seasonal allergic rhinitis, increased from 3.1% to 11.9% between 1964 to 1989 (Ninan 1992). Reasons proposed for the increase in asthma prevalence include heightened community awareness of asthma symptoms, a change in diagnostic labeling patterns amongst health professionals and increase in the severity of illness amongst the same number of asthmatics thus enhancing awareness of symptoms. However, the parallel increase in the prevalence of hayfever (Ninan, Peat 1992) and eczema suggests the importance of exposure to allergens and other environmental factors in the pathogenesis of asthma and allergy. This hypothesis was further supported by a study comparing the prevalence of asthma, allergic disease and atopy between West German and East German schoolchildren by von Mutius and colleagues before the reunification (von Mutius 1994). She found that schoolchildren living in the West German city of Munich had more asthma (9% vs 7%), wheeze (27% vs 17%) and hayfever (9% vs 3%) than those in the East German city of Leipzig. At the same time, West German children were more atopic than East German children (18% vs 8%), with particular respect to mite allergy (4% vs 2%) and pollen allergy (12% vs 3%). The authors concluded that the difference in self-reported asthma and allergic disease could be explained by difference in allergen sensitisation to common inhalants.

As the asthma prevalence was rising over the last two decades, similar increases in asthma mortality and hospital admission rates for asthma have been reported in New Zealand (Sears 1985), United Kingdom (Anderson 1989) and the United States (Halfon 1986). Figure 1 shows that New Zealand and Australia had the highest asthma mortality in the world between 1970 and 1989. The reasons for

the increase in asthma mortality are not entirely clear. Over-reporting of asthma deaths in older subjects was believed to account for some of the high mortality rate in New Zealand (Sears 1986) and Australia (Jenkins 1992) whilst under-reporting of asthma deaths was found in countries where asthma mortality is low (Hunt 1989, Riou 1990). Between 1980 and 1987, the increase in asthma mortality was particularly marked in subjects aged 5 to 34 years with a greater than 40% increase in some countries, i.e. Italy, Denmark, Israel, Australia, France and the United States. On the other hand, decreases in mortality have been noted in New Zealand, Sweden and Japan (Sears 1991).

Figure 1 Asthma mortality in 5-34 age group between 1960 and 1990.



2.4 Asthma Prevalence Studies in Hong Kong

Hong Kong is a westernized city with a population of more than 6 million and a land area of only 1,092 square kilometers. It is one of the most densely

populated cities in the world. It has a subtropical climate and a high temperature and humidity in most months of the year.

2.4.1 ADULT ASTHMA

Data on the prevalence of asthma in adults in Hong Kong is rather limited. In the early 1980s, Fung studied 256 hospital adult patients and medical students and compared them with 500 hospital patients and their relatives in Britain (Fung 1982). He found that asthma and hayfever affected 3% and 2% of Chinese subjects in Hong Kong respectively whilst the prevalence rates were 6% and 9% in the British subjects. On the other hand, rhinitis (18% vs 11%) and eczema (30% vs 7%) were more common in the Chinese than the British subjects. In order to determine if there was an increasing prevalence of asthma, Lai and colleagues studied first year university students at The Chinese University of Hong Kong in 1989 (1,610 subjects, 16-28 years old) and again in 1994 (1,573 subjects, 17-33 years old) using an identical written questionnaire (Lai 1996A). The prevalence of current wheeze, asthma and allergic rhinitis have increased from 4.6% to 7.6%, 4.8% to 7.2% and 24.3% to 38.2% respectively. These findings represented a 65.2% rise in current wheeze and 50% increase in self-reported asthma over a 5 year period. In 1991-1992, a group of 2,032 elderly aged 70 years and over (999 males and 1,033 females) were surveyed by questionnaire, the prevalence rates of asthma and current wheeze were 5% and 8% respectively (Lai 1995). This written respiratory questionnaire consisted of information on symptoms of wheeze, morning chest

tightness, cough etc. There were 56% of the subjects reported at least one respiratory symptom. Total serum immunoglobulin E (IgE) was significantly higher in those with chronic cough and phlegm than those without these complaints in 195 subjects. This study showed that some respiratory symptoms in terms of chronic bronchitis and asthma in Hong Kong elderly were as common as those reported in Sweden and the USA but less than those than in England.

2.4.2 CHILDHOOD ASTHMA

There have been relatively more large epidemiological studies on childhood asthma than that on adult in Hong Kong. This is because of the ease of sampling as the majority of children in the region are attending school. Furthermore, defining asthma in adults especially in the elderly is difficult as diseases such as chronic bronchitis, emphysema and heart disease can be confused with asthma symptoms (Lai 1996A). Ong *et al.* (1991) studied 3,846 primary schoolchildren aged 8-10 years with written questionnaires and respiratory function tests and reported an asthma prevalence of less than 8.0%. In the same study, the investigators compared the prevalence of respiratory symptoms and asthma in children living in the industrial area of Kwai Tsing and the residential area of the Southern District on the Hong Kong Island. They found no difference in asthma prevalence between the 2 groups but more respiratory complaints of cough and sputum production than the former group of children, presumably from exposure to higher levels of ambient air pollutants. Leung *et al.* studied 1,689 schoolchildren aged 7, 12 and 15 years in 1992 using a prototype of the ISAAC questionnaire and reported asthma prevalence

of 10.0%, 8.4% and 7.3% respectively (1994A). The identical questionnaire, appropriately translated, was used to study schoolchildren of the same age groups in Melbourne (Australia), St. Gallen (Switzerland), and La Serena (Chile) (Robertson 1993). Compared to these 3 cities, the asthma prevalence in Hong Kong was slightly higher than that in St. Gallen, about the same as that in La Serena, but was nearly 3 times less than that in Melbourne. In a separate study, Leung & Ho compared the prevalence of asthma and allergic diseases in secondary schoolchildren between Hong Kong, Kota Kinabalu in East Malaysia and San Bu in Guangdong Province, China (Leung 1994B). The schoolchildren were given a questionnaire for parental completion and volunteers underwent skin prick test to determine atopic status. The prevalence rates of asthma, seasonal allergic rhinitis and eczema were found to be highest in Hong Kong (respective rates of 6.6%, 15.7%, 20.1%), intermediate in Kota Kinabalu (respective rates of 3.3%, 11.2%, 7.6%), and lowest in San Bu (respective rates of 1.6%, 2.1% and 7.2%). These findings indicate that there is a genuine difference in asthma prevalence even in areas with similar climate and whose populations are of the same ethnic origin, a finding similar to the West German vs East German study mentioned previously (von Mutius 1994). However, there were virtually no difference in overall atopy rates and skin test positivities to mite, cockroach and cat allergens between the 3 South-East Asian populations of schoolchildren. Thus, allergen sensitization alone could not explain the difference in reported asthma and allergic symptoms.

2.4.3 ASTHMA MORTALITY

The asthma mortality rate in the 5-34 years age group in Hong Kong is considerably less than that reported in New Zealand and Australia but is comparable to that in the United Kingdom and North America. More importantly, it has increased steadily by 90% from 0.52/100 000 in 1980 to a peak of 0.99/100 000 in 1991 (So 1990). The causes for this rise in mortality are largely unexplained but the increase in asthma prevalence and/or severity may contribute. Data from Queen Mary Hospital in Hong Kong also showed a dramatic five-fold increase in asthma admissions in children between 1974 and 1986 (Yeung 1988). Fortunately, consistent with the downward trends reported in other countries, the asthma mortality rates in the 5-34 years age group in New Zealand has remained at 0.3/100,000 (Holtmann 1995) since 1991, possibly related to early diagnosis and prompt treatment with corticosteroid.

2.5 Environmental risk factors for asthma

There are wide variations in the prevalence of asthma among different countries, and among populations of similar ethnic background in various living environment (Leung 1994B, von Mutius 1994) which supports the importance of the living environment for the pathogenesis. The role of the environmental factors was further verified by a migrant study that compared the prevalence of asthma and allergic disease in Asian migrants in Australia with that of the Australian citizens in

Australia as well as Asians living in their home countries (Leung 1994B). In this study, Asian migrants were found to have higher rates of prevalence than their counterparts in Asian countries, but lower than that in Australians. However, the prevalence rates of asthma, wheeze and hayfever increased with the length of stay in Australia in a dose-response fashion. For instance, a 10-years stay in Australia may lead to an increase from 2% to 15% in terms of prevalence of asthma and a rise from 4.8% to 60% in terms of hayfever among those subjects aged 20-40 years when they migrated to Australia. It is therefore possible that the "westernized" and affluent lifestyle may confer certain risks for the development of asthma and allergic diseases. In fact, what exactly modern living and environment factors that are important remain largely unknown but the proposed factors include allergen exposure, indoor and outdoor air pollutants, tobacco smoke exposure, viral infections and dietary factors.

Cockcroft (1988) classified asthma triggers into two major groups in terms of the pathogenesis of asthma: (1) Triggers which cause the contraction of bronchial smooth muscle may also lead to clinica ly significant enhancement of airway responsiveness. These inflammation-inducing triggers include allergens, occupational sensitizing agents, and probably (viral) respiratory tract infection; (2) A number of general triggers that produce immediate bronchial smooth muscle contraction without clinically relevant enhancement of airway responsiveness. These are usually short-lived, such as exercise, cold air, tobacco smoke and irritant gases.

2.5.1 ALLERGENS

Allergens are clinically one of the most important asthma triggers. Allergen exposure is now recognized as the most reliable risk factor for asthma in children (Peat 1996). There is less direct evidence on the association between hyperresponsiveness and exposure to indoor allergens. However, there is strong evidence to suggest an association between high levels of house dust mite exposure and clinical disease (Korsgaard 1983; Hart 1990). In the study done by Korsgaard, the occurrence of mites in dust from homes of patient with asthma was much greater than samples from homes of control subjects. The author confirmed that house-dust mite was a very significant contributing factor to the development of mite-sensitive asthma and there is a clear dose-response relationship. Besides, this difference in exposure corresponded to a relative risk of about 7.0 of clinical asthma. von Mutius (1994) found sensitization to aeroallergens is strikingly more frequent in West Germany than in East Germany, and this finding may be the main cause of the differences in the prevalence of asthma and hay fever between the two parts of the country.

House dust consists of mite antigens that come from various *Dermatophagoides* species. Over the past years, a number of major allergens from the *Dermatophagoides spp*. have been defined. Group 1 allergens (Der p 1, Der f 1, and Der m 1) are 24,000 daltons glycoproteins and are heat stable whilst group 2 allergens consist of 15,000 daltons protein. Although there is extensive cross-

reactivity between Der p 1 , Der f 1, and Der m 1, there is no clear evidence on the structural similarity or cross-reactivity between group 1 and group 2 allergens whatsoever (Platts-Mills 1989). It has been found that Der p 1 levels in homes are influenced by local ambient conditions, i.e. relative humidity of the indoor environment, age of the house, type of heating used, use of feather pillows, the number of occupants, and climate (Peat 1996).

The mite-specific IgE may play a role in the pathogenesis of bronchial asthma in children. In Sweden, asthma was significantly more common in the house dust mite sensitized group than in the atopic control group (Wickman 1991). In this study, house dust mite allergens were found in 40% and 19% of the dust samples of the house dust mite sensitized group and atopic group respectively. A study in Netherlands revealed that exposure to high Der p 1 levels was an important risk factor that increased the severity of asthmatic symptoms in sensitized children (Zock 1994). A dose-response relationship has been demonstrated between the level of allergen and the severity of asthma (Sporik 1992; Peat 1994A). Moreover, by hospitalizing patients in an environment free of house dust mite, an improvement in airway hyperresponsiveness and a reduction in requirement for medication was achieved in a few adults with asthma (Platts-Mills 1982), and serum IgE levels can be reduced by house dust mite avoidance (Gillies 1987). These studies contribute to the accumulating evidence that house dust mite is an important influence on the severity of asthma. In Australia, Dr. Britton *et al.* tested on the same hypothesis (Britton 1986). In this study, although sensitivity to mites was much greater in

coastal New South Wales than in the dry inland areas where mite counts were low, clinical asthma was surprisingly more common inland. This was possibly because the inland subjects had greater prevalence of sensitivity to other allergens such as pollens. Therefore, whilst house dust mite is very important in the development of asthma, other environmental factors may also be important in determining the prevalence of asthma.

In recent years, cockroach has been identified as an important source of indoor aeroallergens in many populations with temperate and tropical climates. The presence of cockroach debris in house dust has been known for a long time. Cockroach infestation is highest in crowded urban areas. Some have suggested that the increased asthma morbidity and mortality rates in inner cities could be related in part to cockroach allergen exposure (Sarpong 1996). In a group of 87 children aged 5 to 17 years with moderate to severe allergic asthma, over 80% of children with bedroom major cockroach allergens (Bla g 1 and Bla g 2) of 1 unit/g or greater demonstrated skin sensitivity to cockroach allergen. Therefore, their results confirmed the high prevalence of sensitization to cockroaches and also emphasized the frequency of combined sensitization to house dust mites.

Pollen allergens are important group of outdoor allergens which can trigger both asthma and hayfever. These allergens are predominantly brought about by wind-pollinated plants (rather than animal-pollinated ones), namely: trees, grass and weeds. The relevant allergens and seasonal fluctuations will vary with locale as well

as climatic conditions. Although grains that are wholly pollinated may have limited access to the lower respiratory tract of the subjects (Busse 1972), the relationship between pollen and clinical asthma has been inevitably recognized (Dolovich 1983). In a study of 5,427 subjects with age of 18 to 65-year-old, prevalence of hay fever symptoms together with a positive skin test to pollen was significantly higher in the exposed (13.6%) vs less exposed community (5.5%) (Charpin 1993). In contrast, prevalence of asthma with positive skin test was 2.5% and 1.9% respectively. Therefore, the author concluded that high exposure to pollen is a risk factor for developing hay fever but not asthma.

Another potential antigen is atmospheric fungal spores. However, its triggering power is less than that of pollen. It may be responsible for autumn or spring/autumn asthma symptoms. Fungi can be found in moist areas such as basements, food storage areas, and waste receptacles (Solomon 1978).

Household animals, particularly cats and dogs, and other small animals (rabbits, hamsters, birds etc.), may release allergens in its secretions(e.g. saliva) or excretions (e.g. urine, faeces). Abdulrazzaq *et al.* (1995) found that the prevalence rate for asthma in children with animals was twice that of children without. A study was done in two climatologically diverse Canadian cities, where researchers investigated the levels of Fel d 1, the major cat allergen in dust from homes of 120 subjects with asthma (Quirce 1995). They found that the highest Fel d 1 level was in home with a cat. In addition, a rather high level were also found in homes of

patients who did not have a cat but visited others with cats. It has been suggested that Fel d 1 can be carried into cat-free building on the clothing of people exposed to cats, as Fel d 1 in garments of people exposed were found to increase with exposure to cats (Enberg 1993). As a result, cat allergen was found in homes of asthmatic patients with and without cat and this may explain the high frequency of cat sensitization among patients with asthma in those two cities (Quirce 1995). Since the exposure to cat allergen may play a role in the symptomatology of many atopic patients, an investigation of sensitization to Fel d 1 should be included in the routine allergologic evaluation of the patients with asthma or perennial rhinitis.

2.5.2 AIR POLLUTION

The harmful effects of air pollution, often resulted from the combustion of petrol and diesel by engines, have been a main public concern in recent years. Although there is no evidence that outdoor air quality was implicated in the increasing prevalence of asthma at a population level, atmospheric air pollution has been linked with impaired lung function, coughs, infections of the lower respiratory tract, and hospital admissions for acute respiratory diseases including asthma.

Cross-sectional studies comparing communities living in polluted and control environments have consistently found adverse respiratory effects in more polluted areas (Charpin 1988, Bericiano 1989). Whilst the concentrations of these pollutants

in the atmosphere have been under more stringent control in many developed countries in recent years, the prevalence of asthma and rhinitis has nevertheless risen to a higher level. In contrast, many developing countries in Asia are more polluted and yet retain low prevalence of these conditions. Indeed, the lack of epidemiological association between air pollution and asthma prevalence in Asia has previously been suggested by Hsieh (1988). He found that despite a fall in pollution in Taiwan between 1974 and 1985 the prevalence of childhood asthma increased by fourfold during the same period. Austin and colleagues (1994) also did not find any associations between atmospheric pollution and the prevalence of asthma in their study in highlands of Scotland. A few studies on asthmatic subjects exposed to O_3, NO_2 and a combination of NO_2 and SO_2 have indicated that these agents increase the airway responsiveness of these individuals to inhaled allergen, and these effects may be maximal 24 h after exposure to the pollutants. Studies investigating the putative mechanisms underlying the effects of these pollutants suggested that exposure to these agents may lead to disturbance of the airway epithelium and release of pro-inflammatory mediators from the epithelial cells, which in turn activates inflammatory cells such as eosinophils (Devalia 1996).

Exhaust fumes from motor vehicle contain particulates, volatile organic compounds, oxides of nitrogen (especially nitrogen dioxide), lead, and sulphur dioxide. Exposure to high levels of air pollutants including sulphur dioxide, nitrogen dioxide, ozone and suspended particulates has long been implicated as a possible cause of respiratory morbidity (Abramson 1991, Utell 1993). Inhalation of both

sulphur dioxide (Sheppard 1981) and nitrogen dioxide (Bauer 1986) could potentiate exercise-induced bronchospasm and maintain bronchial hyperreactivity in asthmatics. It has been hypothesized that prolonged exposure to low levels of sulphur dioxide in the atmosphere can induce airway inflammation and bronchial hyperreactivity whilst intermittent high level of exposure can trigger attacks of asthma similar to house dust mite exposure in mite sensitive individuals (Sheppard 1988, Tseng 1990). The effects of sulphur dioxide can be potentiated by other pollutants such as nitrogen dioxide and ozone (Molfino 1991), which suggests that the combination may be more harmful to health than that of the individual pollutant. Studies on nitrogen dioxide inhalation have shown inconsistent effects on lung function and airway responsiveness. However, a recent study in Finland showed that admissions to hospital with severe asthma correlated with atmospheric levels of nitrogen dioxide (Ruszank 1994).

In addition, ozone is a secondary pollutant formed by the action of sunlight on oxides of nitrogen and volatile organic compounds. Studies of acute inhalation of ozone have shown that ozone significantly increases airway responsiveness and impairs lung function in both asthmatic and non-asthmatic subjects. Molfino *et al.* (1991) has shown that ozone enhances the response to pollen challenge. Therefore, air pollutants can have a potentiation effect on allergen induced bronchial hyperreactivity.

Attention has been focused on the quality and effects of outdoor air. However, it is apparent that people in developed countries would usually spend around 90% of their time indoor (Quackenboss 1982). Nitrogen dioxide, a common indoor pollutant, is one of a number of nitrogen compounds that are by-products of combustion and occur in domestic environments following the use of gas or other fuels for heating and cooking. Indoor concentrations of nitrogen dioxide are maintained by indoor sources, predominantly, gas appliances (Samet 1991). Ambient concentrations are around three times higher in gas-fired houses than in electrically fired homes. During cooking with a gas stove, concentrations of nitrogen dioxide in the kitchen may reach 400 parts per billion (ppb) in a short period (Spengler 1983). Epidemiological data on indoor nitrogen dioxide exposure suggests that it may have a pathogenic role in respiratory disease, especially among children (Hasselblad 1992). From other studies, exposure to an ambient level of NO_2 causes a delayed effect on bronchial responsiveness in asthmatics (Strand 1996).

Some experimental data has also shown an increase in the non-specific bronchial reactivity of normal subjects as well as asthmatic subjects (Tunnicliffe 1994). Two recent reports described that NO_2 alone and in combination with SO_2, at concentrations that may be encountered in daily life, enhance the bronchoconstrictive response to inhaled house dust mite in patients with mild asthma. Neither of these latest experimental studies allows estimation of the clinical magnitude of the

reported functional change, although Tunicliffe *et al.* suggested that these effects were likely to be small (Antó 1995).

2.5.3 Environmental Tobacco Smoke (ETS)

Some studies have documented that maternal smoking during pregnancy is associated with an increased risk of pre-term delivery (Kelly 1995), lower birthweight (Conter 1995), increased hospitalization in early life (Chen 1994), and caused significant reductions in airway size in otherwise healthy infants (Brown 1995). These effects may lead to the subsequent development of asthma (Kelly 1995). Smoking by fathers or maternal caregivers also has been found to be significantly associated with bronchial asthma in schoolchildren (Al Frayh 1989, Ehrlich 1992). In addition, exposure to ETS in early childhood increases the risk of recurrent wheeze at the age of 7 to 12 years in non-allergic children and allergic girls (Henderson 1995). The effect in allergic boys may be minor as compared with the more dominant effects of allergen exposure and may be more difficult to detect.

ETS has been associated with airway hyperresponsiveness in a number of population surveys as well as in many clinical studies. The association is stronger in older subjects or in subjects with a greater lifetime exposure to cigarettes. Reduced lung function has also been recorded in adult asthmatic patients who are exposed to ETS (Jindal 1994). Murray and Morrison (1986) reported that airway

responsiveness was found more commonly in the children of smoking parents. However, there is little evidence that smoking among adults leads to any increased risk of developing asthma. The effect of ETS on airway responsiveness in children is still not clear. One study found no effect of ETS on BHR despite an increase in the prevalence of asthma in 7- to 13-year-olds (Soyseth 1995), whilst another study found a significant effect on BHR to exercise challenge at 9 to 14 years, especially if the duration of exposure to ETS was more than 9 years and if the cumulative exposure was high (Agudo 1994).

Wheeze and asthma are likewise more frequent among children exposed to ETS (Zmirou 1990). Moreover, the increase of reported physician-diagnosed asthma was significantly associated with exposure to ETS at work (Dekker 1991, Flodin 1995). The published studies that have examined the consequences of exposure to environmental tobacco smoke in children with asthma have relied exclusively on parents' reports of their smoking habits. The presence of smokers in the home was found to be an important risk factor on the diagnosis of asthma (Soto 1994). The association of passive smoking with dyspnea, wheeze, and asthma observed a dose-dependent increase in respiratory symptoms with hours per day of exposure (Leuenberger 1994). Even reliable parental reports of exposure to environmental tobacco smoke could be a relatively inaccurate measure of children's actual inhalation of such smoke. Although this inaccuracy is not likely to interfere with analyses comparing exposed and unexposed groups, it could make it difficult to detect a dose-response relationship. Chilmonczyk *et al.* (1993) used urinary cotinine

levels of the subjects to measure actual exposure. Although their results showed discrepancies between parental reports and cotinine measurements, the data emphasized the need to stop the exposure of children with asthma to environmental tobacco smoke.

2.5.4 VIRAL INFECTIONS

Although viral infections are associated with the majority of asthma exacerbations in school age children, the role of respiratory infections in early life on the later development of asthma is not well understood. Empey and co-workers (1976) monitored changes in airway reactivity in 12 young normal subjects with a clinically uncomplicated viral URI (upper respiratory illnesses). Bronchial reactivity was measured by the change in airway resistance to a histamine aerosol. When compared to non-infected controls, subjects with colds had significantly greater increases in airway resistance to aerosol histamine (218+/- 54.6% vs 30.5+/- 5.5%), and airway hyperreactivity persisted for up to 6 weeks in some subjects. Although a number of earlier studies suggested that early respiratory infections are important factors for the presence of asthma or BHR in later childhood, whether such infections predispose to later illness or are the first expressions of airway illness has not been resolved (Peat 1996). More recently, Martinez (1994) suggested a contradictory hypothesis that an inverse relationship exists between respiratory infection in early life and the development of asthma. Viruses may influence the determination of T helper phenotypes during the months after birth when the

immune system is immature and amenable to change. This hypothesis is supported by data showing German children who are exposed to early infection as a result of having older siblings have a reduced rate of atopy and a similar inverse relationship exists between number of siblings and hay fever in English children (Strachan 1989).

2.5.5 DIETARY FACTORS

In recent years, the average diet has changed in affluent countries, with increasing intake of processed foods, salt, polyunsaturated oils, and a lower consumption of fresh foods. This change may have played a role in the higher rates of childhood asthma (Peat 1994B). Although direct evidence is poor, it has been suggested that a diet which contains chemical additives and preservatives may be a factor to increase in asthma in affluent countries (Gregg 1986). Accordingly, a number of studies are investigating the effects of specific dietary factors on symptoms, BHR, and lung function. In the United Kingdom, a high magnesium intake was found to be associated with improved lung function, a reduction in BHR (odds ratio, 0.8; 95% CI, 0.72 to 0.93), and self-reported wheeze (odds ratio = 0.9; 95% CI: 0.76 to 0.95) in a large sample of adults (Britton 1994). It has also been suggested that an increased salt intake is associated with increased asthma mortality and airway hyperresponsiveness in men (Peat 1995). Clinical studies have been unable to demonstrate an effect on morbidity. The severity of asthma, as assessed by peak expiratory flow rate, did not change after 2 weeks of altered salt intake (Pistelli

1993). Cockcroft *et al.* (1993) investigated the role of table salt in their study in Italy. They found that table salt use was associated with increased respiratory symptoms and airway responsiveness in boys aged 9-16 years. Lung function has been related to antioxidant vitamin intake, which is biologically plausible because antioxidants may alter airway inflammation by protecting the cell membrane, and may confer a small protective effect. However, in the United States, no association was found between subjects intake level of vitamin A and measurements of airway obstruction (Shahar 1994). Besides, in the United Kingdom, high salt intake was not found to be associated with BHR or allergic symptoms in adults (Britton 1994).

Peat *et al.* showed that children who eat fish more than once a week are at reduced risk of having BHR and asthma (Peat 1995). There are both theoretical and circumstantial evidence suggesting that dietary fish oils can alter inflammatory responses in the airways, especially in subjects who have mild disease (Peat 1994B). This is a plausible concept because oily fish provides an important source of omega-3 oils, which play an anti-inflammatory role in cell metabolism (Lee 1986).

The independent effects of different dietary factors may be very difficult to analyse and assess from questions on recent diet and may be confounded by preferential dietary supplementation in certain high-risk groups. Besides, dietary effects may also be more difficult to detect in adults who are likely to have already

developed a chronic respiratory status when compared with children whose lungs are developing and in whom diet is likely to have more influence (Peat 1996).

2.5.6 ALLERGEN AVOIDANCE

The asthma-allergy connection can be indirectly assessed by allergen avoidance studies whereby allergen exposure is reduced in sensitised subjects to demonstrate if clinical improvement occurs. Studies of dust mite avoidance have clearly been associated with a reduction both in asthma symptoms and non-specific bronchial hyperresponsiveness. Platts-Mills *et al.* (1982) showed marked improvements in asthma symptoms and bronchial hyperresponsiveness in dust sensitive asthmatics when they stayed in the "allergen free" environment in hospital for a 2 to 3 months period. Admission to institutions at high altitudes where house dust mite and other allergens are scarce has produced improvement in symptoms and medication scores (Warner 1988). At the same time, a number of studies have examined a variety of avoidance procedures such as using occlusive coverings over beds and pillows, hot washing of bedding, removal of bedroom carpets and chemical acaricides to reduce and prevent mite colonization, and to treat and remove mite allergens. In particular, Korsgaard utilised domestic climate control to reduce absolute humidity using ventilation and heat recovery systems to lower indoor absolute humidity below 7g of water vapour/kg of dry air, a level believed to be critical for mite growth (Korsgaard 1982, Harving 1988). Despite the lack of control groups and the employment of multiple avoidance measures in some studies, it is concluded the dust mite avoidance measures lead to reduction of mite allergen

concentrations (Owen 1990) and clinical improvement in asthma symptoms and bronchial hyperresponsiveness (Murray 1983).

Cats are the source of another important indoor allergen that can produce small airborne small particles. Removing or weekly washing the animal and the use of high-efficiency particulate air filters for air ducts and vacuum cleaners are useful in reducing dust mite and cat allergens (Squillace 1992).

There is no evidence to show that open windows could reduce the level of indoor allergens. In a study that compared the homes with and without air-conditioning, the total indoor spore counts showed significant reduction in all indoor locations of air-conditioned homes. There is suggestion that the major mechanism in reducing spore counts in air-conditioned homes is the closed windows, although the lower relative humidity and perhaps filtration are also associated with lower spore counts (Hirsch 1978). Control studies within normally ventilated rooms and outside their open windows showed a marked but variable inward flux of outdoor particles (Solomon 1980).

Chapter 3 Epidemiological survey

This thesis consists of two parts. The first part is the epidemiological survey - the ISAAC study. The ISAAC study is a cross-sectional survey of asthma and allergic diseases in schoolchildren aged 13-14 years using both written and video questionnaires. Nested within the ISAAC study is a validation study of the video questionnaire used in ISAAC against BHR, an objective measure of asthma. The second part is an environmental survey - a study of the indoor environment of residential homes in Hong Kong to define its relevance to asthma and allergic disease. The methods used in the two surveys were different and will be discussed separately.

3.1 Subjects and methods

3.1.1 SUBJECTS

According to the ISAAC protocol, schoolchildren of the age of 13-14 years were targeted for the study. There were a total of 400 secondary schools with approximately 110,000 schoolchildren of the target age range in Hong Kong. Forty of these schools were not eligible for the study as these schools have less than 100 children in the target age group. A list of the suitable secondary schools was

generated by computer randomization out of 360 schools in Hong Kong. Of the first 15 listed schools that were contacted, 13 agreed to participate. These schools were distributed in different districts throughout the territory and there were 4,800 registered students in the target age group of 13-14 years old. An introduction letter and consent forms were sent to the parents of these 4,800 schoolchildren and 4,677 consented to participate, representing an overall response rate of 92.7%.

3.1.2 WRITTEN QUESTIONNAIRE

The selected schools were visited sequentially during regular schooldays. Each subject was given an ISAAC written questionnaire for completion followed by the video questionnaire at the same session in school. The written questionnaire has been translated from English into Chinese in accordance with the standard ISAAC protocol. This involved an independent person who was bilingual and familiar with translation from English to Chinese. This was then translated back into English by another bilingual person. The translated questionnaire was tested out in a group of teenagers aged 13-14 years and necessary modifications were made before the survey was carried out. During the survey at schools, written questionnaires were completed first before the video questionnaires to avoid potential order bias. The ISAAC written questionnaires asked for information on demography, symptoms of wheeze, asthma, rhinitis and eczema. Additional questions on active and passive smoking, and parents' education level were also included. The full questionnaire is shown in Appendix 1. Particular attention was focused on the five questions that

corresponded to the 5 scenes in the video questionnaire (see below):

1. Have you had wheezing or whistling in the chest in the last 12 months?

2. In the last 12 months, has your chest sounded wheezy during and after exercise?

3. In the last month, how often, on average, has your sleep been disturbed by your own wheezing?

4. In the last 12 months, have you experienced dry cough at night, apart from the ones associated with a cold or chest infection?

5. In the last 12 months, has wheezing ever been severe enough to limit your speech to only one or two words?

3.1.3 VIDEO QUESTIONNAIRE

The video questionnaire consists of audiovisual presentation of common asthmatic symptoms or events. The standard ISAAC video questionnaire (VQ) is made up of 5 sequences of asthmatic symptoms/events demonstrated by children and adolescents of various ethnic groups. The first 3 sequences reveal various scenes of wheezing whereas the final 2 sequences show other asthmatic symptoms (Table 2). The students were given a one-page questionnaire in Chinese and were asked if they had experienced similar symptoms to the ones shown on the video. The questions were both displayed and subtitled in Chinese on the screen. The video runs for 7 minutes and there is a 15 second interval to answer the questions after each

Table 2 The ISAAC Video Questionnaire (VQ)

The video scenes	The questions after each video scene
1. Moderate wheezing at rest (a Caucasian girl)	Has your breathing ever been like this at
2. Wheezing and shortness of breath after exercise (a black African boy)	any point of time in your life before? YES/NO
3. Waking up at night with wheezing (a Caucasian girl)	If 'YES', did it happen in the last 12 months? YES/NO
4. Waking up at night with coughing (a Chinese boy)	If 'YES', did it happen once or more per month? YES/NO
5. Severe attack of asthma with difficulty in breathing at rest (an Indian girl)	

scene. The term "asthma" was not mentioned in the program until the 5 sequences had been shown.

3.1.4 BRONCHIAL HYPERRESPONSIVENESS TESTING (BHR)

In order to validate the video questionnaire, one hundred and eighty-nine children randomly recruited from a secondary school in Hong Kong were asked to undergo BHR testing. They were all ethnic Chinese and their mother tongue was Cantonese, a dialect in Southern China. They were 12-18 years old (mean age: 13.6 years) and 112 were boys (59.3%).

All 189 subjects underwent the video questionnaire prior to the bronchial challenge with inhaled methacholine according to the protocol reported by Yan *et al.* (1983), which is known to be a rapid and reproducible method. BHR is defined as having a provocation dose of methacholine causing a 20% fall in FEV_1 from baseline (PD_{20}) of ≤ 6.12 μmol methacholine.

1 Equipment

a) Lung Function

A spirometer with an attached printout of volume against flow is used (Vitalograph Medical Instrumentation Ltd., Buckingham, England). The operator and subject are able to see the forced expiratory tracings. Reproducible values for

the forced expiratory volume in first second (FEV_1) are essential.

b) Nebulisation of Methacholine

This is done with a De Vilbiss No. 40 hand-held nebuliser because it is simple, cheap and portable. It is tested for output by placing methacholine solution in the nebulisers. The mean output is 0.003 ml with a range of 0.0018 and 0.0042 ml.

c) Methacholine Solution

One gram of methacholine chloride is weighed out carefully and quickly to minimize exposure to air and moisture. Twenty mls of normal saline is added to give a 5% solution, further aliquots are diluted with normal saline to give solutions of 2.5%, 0.62% and 0.31% concentration. The methacholine chloride powder is stored under airtight conditions in the freezer to minimize exposure to air and moisture.

2 Initial Lung Function

The forced expiratory curves are recorded until reproducible tracings are achieved and the largest value for FEV_1 and the forced vital capacity (FVC) are recorded. Students' heights are measured and their predicted lung function for age and height are calculated (Lam 1982). If the FEV_1/FVC is greater than 50% and the FVC greater than 60% of the predicted value for the individual, then an inhalation test can proceed. If the spirometric function is less than this criteria, the BHR test

will not be performed.

3 Methacholine Inhalation Test (appendix 2)

If the subject has taken bronchodilator in the previous 6 hours or oral bronchodilator therapy in the previous 12 hours, the challenge is postponed to another occasion. Two different dose schedules are outlined - one for those subjects who has a history of asthma (Challenge A) and the other for those whose lung function is entirely normal and who has no history suggestive of asthma (Challenge B).

4 Procedure

1) Decide if the subject is to have Challenge A (asthmatic) or Challenge B (normal).

2) Place approximately 1 ml of normal saline in a clearly labeled De Vilbiss nebuliser and use it as a control solution. The mouthpiece of the nebuliser is placed close to the subject partly open mouth. At the beginning of the inspiration the operator gives the bulb of the nebuliser one firm squeeze. The subject then holds his breath for 4 - 5 seconds. This process is done a few times until the subject has mastered this technique.

3) Spirometric function is measured one minute after the inhalation.

Reproducible values (to within 0.2 L for FEV_1) are required.

4) Challenge in the same way as with the normal saline, starting with one inhalation of either 0.31% (Challenge A) or 0.6% (Challenge B) as shown in the Chart of Methacholine Doses. Some doses require more than one inhalation and these should be given in consecutive inspiration.

5) The challenge is stopped when the FEV_1 has fallen by 20% or more from the pre-challenge (post-saline) value or dose 8 has been given.

6) If the FEV_1 fell by more than 10% it is usual to give a bronchodilator aerosol to aid recovery.

5 Analysis of Data

The FEV_1 value after each dose is read from the tracing and the percentage change from the post-saline value is plotted against the administered dose of methacholine on a log scale as shown in the diagrams (appendix 3 & 4). The dose of methacholine which causes a 20% fall is read as PD_{20}. Subjects whose FEV_1 do not drop by 20% or more from baseline even after inhalation of the highest dose of methacholine were considered normo-responsive.

3.2 Result-epidemiological survey

Table 3 showed the responses to the written questionnaire. Completed questionnaire response were obtained from 4,665 subjects of which 49.8% were boys. The majority (62.4%) was between 13-14 years, whilst 30.6% was more than 15 years and only 7% was 11-12 years. Asthma ever, wheeze ever and current wheeze were reported by 11.2%, 19.5% and 12.4% of schoolchildren respectively and the prevalence rates were more common in boys than girls ($p<0.001$). More than one tenth (12.3%) of subjects reported at least one wheezing attack per month in the group with current wheeze. Moreover, 3.8% had at least weekly sleep disturbance by wheeze in the 12 months before the study. With regard to the question " severe wheeze limiting speech in past 12M ", 2.2% of boys had positive answers compared with 2.6% girls with a total prevalence of 2.4%. Nearly 30% of schoolchildren reported exercise induced wheeze (29.6% for boys and 28.6% for girls). Current nocturnal cough was common in both sex affecting 27.8% of subjects.

Rhinitis was the most common allergic disease affecting 52.1% of subjects and was more common in female (53.9% vs 50.2%, $P = 0.01$). In particular, it was reported by 70.0% of wheezers and 68.8% of children with a history of asthma ever. The majority of rhinitis sufferers had perennial symptoms. Compared with the prevalence of rhinitis, only 4.7% of subjects had hayfever ever or seasonal rhinitis. A total of 707 (15.2%) of respondents reported eczema ever but only 156 of them (3.3%) had an itchy rash affecting the flexural areas in the past 12 months.

Table 3. Response from subjects to Written Questionnaire

	Boys		Girls		Total	
	%	95% CI	%	95% CI	%	95% CI
Sex	49.8		50.2		100	
Age						
11-12 years	7.0		7.8		7.4	
13-14 years	62.4		66.0		64.2	
≥15 years	30.6		26.2		28.4	
Asthma ever	13.1	11.7 - 14.4	9.3	8.1 - 10.4	11.2	10.3 - 12.1
Wheeze ever	23.3	21.6 - 25.0	15.8	14.3 - 17.2	19.5	18.4 - 20.6
Wheeze in past 12M	14.3	12.9 - 15.7	10.5	9.2 - 11.7	12.4	11.4 - 13.3
No. of wheezing attacks in past 12M						
1-3 episodes	10.4	9.1 - 11.6	5.2	4.3 - 6.1	8.5	7.7 - 9.3
4-12 episodes	2.6	1.9 - 3.2	3.1	2.4 - 3.8	2.9	2.4 - 3.3
>12 episodes	1.6	1.1 - 2.1	1.5	1.0 - 1.9	1.5	1.2 - 1.9
No. of episodes of sleep disturbance by wheeze in past 12M						
<1 per week	4.5	3.6 - 5.3	3.6	2.9 - 4.4	4.1	3.5 - 4.6
>1 per week	0.5	0.2 - 0.8	0.4	0.2 - 0.7	0.5	0.3 - 0.7
Severe wheeze limiting speech in past 12M	2.2	1.6 - 2.7	2.6	1.9 - 3.2	2.4	1.9 - 2.8
Exercise induced wheeze in past 12M	29.6	27.8 - 31.5	28.6	26.8 - 30.5	29.1	27.8 - 30.4
Nocturnal cough in past 12M	25.2	23.4 - 27.0	30.3	28.4 - 32.2	27.8	26.5 - 29.0

Table 3. Response from subjects to Written Questionnaire (con'd)

	Boys		Girls		Total	
	%	95% CI	%	95% CI	%	95% CI
Rhinitis ever	50.2	48.2 - 52.3	53.9	51.9 - 55.9	52.1	50.6 - 53.5
Rhinitis in past 12M	41.9	39.9 - 43.9	46.9	44.9 - 48.9	44.4	43.0 - 45.8
Rhinoconjunctivitis in past 12M	23.7	22.0 - 25.4	28.9	27.1 - 30.8	26.3	25.1 - 27.6
Rhinitis affecting daily activities ever						
Little	30.7	28.8 - 32.5	31.0	29.1 - 32.9	30.8	29.5 - 32.2
Some	3.5	2.8 - 4.3	3.9	3.1 - 4.7	3.7	3.2 - 4.3
Severe	0.9	0.5 - 1.2	0.6	0.3 - 0.9	0.7	0.5 - 0.9
Hayfever ever	5.0	4.1 - 5.9	4.4	3.6 - 5.3	4.7	4.1 - 5.3
Itchy rash ever	5.2	4.3 - 6.1	5.6	4.7 - 6.5	5.4	4.8 - 6.1
Itchy rash in past 12M	4.3	3.4 - 5.1	4.7	3.8 - 5.5	4.5	3.9 - 5.1
Itchy flexural rash in past 12M	3.6	2.8 - 4.3	2.7	2.0 - 3.3	3.1	2.4 - 3.8
Clearance of Rash in past 12M	4.5	3.7 - 5.4	3.8	3.0 - 4.6	4.2	3.6 - 4.7
Night waking by rash in past 12M						
<1 night per week	2.8	2.2 - 3.5	2.6	2.0 - 3.3	2.7	2.3 - 3.2
>1 night per week	0.4	0.2 - 0.8	0.6	0.3 - 1.0	0.5	0.3 - 0.7
Eczema ever	13.8	12.5 - 15.3	16.5	15.0 - 18.0	15.2	14.1 - 16.2

There were similar number of subjects with current itchy rash (4.5%) as those who had lost the symptoms in the past year (4.2%). Night disturbance by itchy rash was uncommon and affected 0.5% of schoolchildren only.

There are 5 groups of questions included in the VQ as shown in table 4. Nearly 30% reported " nightwaking with cough ever ", the prevalence rate was higher in girls (33.5%) than in boys (26.1%, $p<0.001$). In contrast, only 5.5% had nightwaking with wheeze ever, a scene acted by a Caucasian girl. More than 20% had wheeze induced by exercise and wheeze ever was present in 13.7% whilst 10% had wheeze in the past 12 months. Amongst the 9.7% of children who had experienced severe asthma, 71.1% had current severe asthma attack and 21.6% had episodes at least monthly in the 12 months prior to the survey. Compared to girls, boys complained of more symptoms of wheeze at rest, exercise induced wheeze and nocturnal wheeze in the past year than girls ($p < 0.05$).

Table 5 showed the correlation of selected risk factors with current wheeze and severe wheezing attack that were calculated by univariate logistic regression. In both video and written questionnaire, boys had more complaints of current wheeze than girls (OR = 1.42, 95% CI: 1.19-1.70). Other important risk factors remained significant with similar odds ratios by written questionnaire for current wheeze included current rhinitis (OR = 3.07, 95% CI: 2.55-3.70), current eczema (OR = 2.93, 95% CI: 2.04-4.19), and active smoking (OR = 1.98, 95% CI: 1.39-2.82); for severe wheeze also included current rhinitis (OR = 2.90, CI: 1.93-4.37), current eczema (OR = 7.14, CI: 4.28-11.93) and active smoking (OR = 4.15, CI: 2.25-7.68).

Table 4. Responses to Video Questionnaire

	Boys		Girls		Total	
	%	95% CI	%	95% CI	%	95% CI
Wheeze at rest ever	14.9	13.4 - 16.3	12.4	11.1 - 13.8	13.7	12.7 - 14.6
Wheeze at rest in past 12M	11.1	9.8 - 12.4	8.9	7.8 - 10.1	10.0	9.1 - 10.9
Wheeze at rest ≥1 per month	4.2	3.4 - 5.0	3.1	2.4 - 3.8	3.7	3.1 - 4.2
Wheeze after exercise ever	24.0	22.3 - 25.8	19.1	17.5 - 20.7	21.5	20.4 - 22.7
Wheeze after exercise in past 12M	17.2	15.7 - 18.8	13.4	12.0 - 14.8	15.3	14.3 - 16.4
Wheeze after exercise ≥1 per month	9.4	8.2 - 10.6	7.4	6.3 - 8.5	8.4	7.6 - 9.2
Nightwaking with wheeze ever	6.7	5.7 - 7.7	4.4	3.5 - 5.2	5.5	4.9 - 6.2
Nightwaking with wheeze in past 12M	4.8	3.9 - 5.7	2.8	2.1 - 3.4	3.8	3.2 - 4.3
Nightwaking with wheeze ≥1 per month	1.2	0.8 - 1.7	0.8	0.4 - 1.2	1.0	0.7 - 1.3
Nightwaking with cough ever	26.1	24.3 - 27.9	33.5	31.6 - 35.4	29.8	28.5 - 31.1
Nightwaking with cough in past 12M	21.8	20.1 - 23.5	27.2	25.4 - 29.0	24.5	23.3 - 25.7
Nightwaking with cough ≥1 per month	4.9	4.0 - 5.7	3.8	3.1 - 4.6	4.4	3.8 - 4.9
Severe asthma attack ever	9.7	8.5 - 10.9	9.7	8.5 - 10.9	9.7	8.8 - 10.5
Severe asthma attack in past 12M	6.8	5.8 - 7.8	7.1	6.1 - 8.1	6.9	6.2 - 7.7
Severe asthma attack ≥1 per month	2.0	1.3 - 2.8	2.2	1.6 - 2.8	2.1	1.7 - 2.5

Table 5. **Selected Risk Factors for Current Wheeze & Severe Wheeze Limiting Speech in the Past 12 months by Univariate Logistic Regression. Values are odds ratios and 95% confidence intervals.**

	Written Questionnaire				Video Questionnaire			
	Current Wheeze		Severe Attack		Current Wheeze		Severe Attack	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age								
11-12 years	1.00	----	1.00	----	1.00	----	1.00	----
13-14 years	1.08	0.77 - 1.53	0.86	0.42 - 1.74	1.00	0.69 - 1.46	0.91	0.60 - 1.37
>14 years	1.11	0.77 - 1.60	1.02	0.48 - 2.14	1.08	0.73 - 1.60	0.80	0.51 - 1.26
Sex								
Female	1.00	----	1.00	----	1.00	----	1.00	----
Male	1.42	1.19 - 1.70	0.84	0.57 - 1.22	1.27	1.05 - 1.54	0.95	0.76 - 1.20
Rhinitis in past 12M								
No	1.00	----	1.00	----	1.00	----	1.00	----
Yes	3.07	2.55 - 3.70	2.90	1.93 - 4.37	2.23	1.83 - 2.71	2.28	1.81 - 2.88
Itchy flexural rash in past 12M								
No	1.00	----	1.00	----	1.00	----	1.00	----
Yes	2.93	2.04 - 4.19	7.14	4.28 - 11.93	2.62	1.77 - 3.88	3.89	2.60 - 5.82

Table 5. **Selected Risk Factors for Current Wheeze & Severe Wheeze Limiting Speech in the Past 12 months by Univariate Logistic Regression. Values are odds ratios and 95% confidence intervals (cond)**

	Written Questionnaire				Video Questionnaire			
	Current Wheeze		Severe Attack		Current Wheeze		Severe Attack	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Father's education								
≤Form 3	1.00	----	1.00	----	1.00	----	1.00	----
Form 4 - Form 7	1.03	0.80 - 1.31	1.15	0.66 - 2.01	1.26	0.96 - 1.63	1.09	0.78 - 1.53
≥College	1.27	0.94 - 1.72	1.04	0.49 - 2.21	0.96	0.66 - 1.38	1.44	0.96 - 2.15
Mother's education								
≤Form 3	1.00	----	1.00	----	1.00	----	1.00	----
Form 4 - Form 7	1.17	0.93 - 1.49	1.13	0.65 - 1.99	1.24	0.96 - 1.61	1.43	0.95 - 1.95
≥College	1.33	0.89 - 1.99	2.05	0.93 - 4.51	1.19	0.75 - 1.89	1.38	0.80 - 2.40
Active smoking								
No	1.00	----	1.00	----	1.00	----	1.00	----
Yes	1.98	1.39 - 2.82	4.15	2.25 - 7.68	1.31	0.85 - 2.01	1.07	0.61 - 1.88
Passive smoking								
No	1.00	----	1.00	----	1.00	----	1.00	----
Yes	1.14	0.92 - 1.42	1.05	0.64 - 1.74	0.96	0.76 - 1.23	0.97	0.72 - 1.31

Current rhinitis was significantly associated with current wheeze (OR = 3.07, 95% CI: 2.55-3.70) and severe wheezing attack (OR = 2.90, 95% CI: 1.93-4.37). In particular, the participants who suffered from current eczema were 7 times more likely to report severe wheezing attack by written questionnaire. Active smoking was associated with current wheeze (OR = 1.98, 95% CI: 1.39-2.82) and severe attack (OR = 4.15, 95% CI: 2.55-7.68) by written questionnaire but not in the video questionnaire. On the other hand, age, parental education and passive smoking were not important factors in this survey.

Table 6 showed the direct cross-tabulation between the two questionnaires for each question. Concordance was estimated by identical responses to the 5 paired questions in both the written and video questions, namely "Wheezing", "Exercise wheeze", "Nocturnal wheeze", "Nocturnal cough", "Severe wheeze". Overall, correlation of responses to the 5 corresponding questions was good, with concordance rate ranging from 66.1% for the questions on "nocturnal cough" to 91% for the questions on "severe wheeze".

A total of 189 students underwent BHR testing as well as VQ. There were 16 (8.5%) who were hyperresponsive to methacholine with a PD_{20} of < 6.12 μmol. 14 of the 32 students (43.8%) with diagnosed asthma were hyperresponsive and they comprised the majority of students with BHR (87.5%). The result is reliable and valid because the majority of the subjects were 13-14 years old and the mean age was 13.6, the target subjects of ISAAC. Furthermore, there is no evidence that BHR will change significants within the age range tested.

Table 6 Concordance between the video (VQ) and written (WQ) questionnaires.

Video questionnaire	Yes	Yes	No	No	Concordance
Written questionnaire	Yes	No	Yes	No	
Wheezing	17 (9.0%)	13 (6.9%)	17 (9.0%)	142 (75.1%)	84.1%
Exercise wheeze	29 (15.3%)	25 (13.2%)	17 (9.0%)	118 (62.4%)	77.8%
Nocturnal wheeze	2 (1.1%)	17 (9.0%)	10 (5.3%)	160 (84.7%)	85.7%
Nocturnal cough	31 (16.4%)	35 (18.5%)	29 (15.3%)	94 (49.7%)	66.1%
Severe wheeze	3 (1.6%)	2 (1.1%)	15 (7.9%)	169 (89.4%)	91.0%

The sensitivity, specificity and Youden's index (Youden 1950) of the corresponding questions in the video and written questionnaires were shown in table 7 with BHR as the predicted standard. Youden's index is the sum of the sensitivity and specificity minus one, and thus place equal weight on each measure. Youden's index is a particularly appropriate measure for validity of instruments on prevalence surveys because it provide an estimate of the extent to which the observed difference in prevalence between the two populations is reduced by imperfect sensetivity and specificity of the instrument (Burney 1989). The highest predictive value of BHR by the Youden's index was 0.78 for the question on "asthma ever" in the WQ when compared with all the questions on asthma symptoms in both questionnaires. Amongst the 5 paired questions in WQ and VQ, question 2 on "exercise wheeze" in VQ had the highest Youden's index of 0.49 compared to the lowest one, question 4 on "nocturnal cough" (0 and 0.03 for VQ and WQ respectively). For the question on "severe wheeze", Youden's index for the video questionnaire was significantly higher than that for the written questionnaire (0.44 vs 0.11, $p<0.05$). Except for this significant difference, other responses between corresponding questions in the video and written questionnaires had similar Youden's indices for BHR.

Table 8 illustrated the ability of questions from the VQ and WQ to predict BHR. Escalating number of positive responses to the questions of VQ and WQ improved the specificity (VQ: from 0.53 to 0.97; WQ: from 0.52 to 0.97) but reduced the sensitivity for BHR (VQ: from 0.94 to 0.25; WQ: from 0.75 to 0.13). The highest Youden's index in the "more than one question positive" was still lower than the highest one seen for single question "exercise wheeze" in the video

questionnaire (0.47 vs 0.49). Similarly, the question on "current wheeze" in the WQ had the highest Youden's index (0.44) comparing with all combinations of positive responses of the 5 questions. In conclusion, the best Youden's index for any question indicates that it has the highest predictability for BHR and the predictive value is not enhanced by increasing the number of positive responses to additional questions.

Table 7. Ability of WQ and VQ questions to predict BHR (n=189). Values are 95% confidence intervals.

Question	Questionnaire	Sensitivity	Specificity	Youden's index	p*
1. Wheezing	WQ	0.56(0.31-0.79)	0.88(0.82-0.92)	0.44(0.19-0.69)	ns
	VQ	0.56(0.31-0.79)	0.86(0.79-0.90)	0.42(0.17-0.67)	
2. Exercise wheeze	WQ	0.56(0.31-0.79)	0.74(0.67-0.80)	0.30(0.05-0.55)	ns
	VQ	0.69(0.42-0.88)	0.80(0.73-0.85)	0.49(0.25-0.72)	
3. Nocturnal wheeze	WQ	0.38(0.16-0.64)	0.93(0.87-0.96)	0.31(0.06-0.54)	ns
	VQ	0.31(0.12-0.59)	0.96(0.92-0.98)	0.27(0.04-0.50)	
4. Nocturnal cough	WQ	0.38(0.16-0.64)	0.65(0.58-0.72)	0.03(0.00-0.13)	ns
	VQ	0.31(0.12-0.59)	0.68(0.61-0.75)	0.0(-0.24-0.23)	
5. Severe wheeze	WQ	0.13(0.02-0.40)	0.98(0.95-1.00)	0.11(0.00-0.27)	<0.05
	VQ	0.50(0.26-0.75)	0.94(0.89-0.97)	0.44(0.20-0.96)	
6. Asthma ever	WQ	0.88(0.60-0.98)	0.90(0.84-0.94)	0.78(0.60-0.94)	

*Comparison between the Youden's indices of WQ and VQ by paired t test.

Table 8 : Ability of ISAAC video (VQ) and written questions (WQ) to predict BHR

	Sensitivity	Specificity	Youden's index
VQ: more than one question positive	0.94(0.68-1.00)	0.53(0.46-0.61)	0.47(0.33-0.61)
more than two questions positive	0.63(0.36-0.84)	0.82(0.75-0.87)	0.45(0.20-0.69)
more than three questions positive	0.44(0.21-0.69)	0.93(0.87-0.96)	0.37(0.12-0.61)
more than four questions positive	0.25(0.08-0.53)	0.97(0.92-0.99)	0.22(0.00-0.43)
WQ: more than one question positive	0.75(0.47-0.92)	0.52(0.44-0.60)	0.27(0.05-0.50)
more than two questions positive	0.63(0.36-0.84)	0.78(0.71-0.84)	0.41(0.16-0.65)
more than three questions positive	0.50(0.26-0.75)	0.91(0.86-0.95)	0.41(0.17-0.66)
more than four questions positive	0.13(0.02-0.40)	0.97(0.92-0.99)	0.10(-0.07-0.26)

3.3 *Discussion-epidemiological survey*

There is an increasing trend of asthma prevalence worldwide. Research in asthma prevalence in Hong Kong is necessary in order to confirm the rising trend and to compare the prevalence with other countries. Asthma epidemiological studies are difficult to compare due to the variable definitions, differences in methodologies used and the numerous confounding risk factors assessed. ISAAC is a large international study and involved a large number of schoolchildren from regions with both high and low asthma prevalence and morbidity, thus the data generated is a reliable estimate owing to the utilization of identical method.

In our study, asthma prevalence in Hong Kong was found to be higher than that in previous studies. For the international comparison, two school years were selected which included students with the greatest proportion of 13 years olds and 14 years old, the target subjects of ISAAC, according to the ISAAC protocol. From the ISAAC study, it was found that the prevalence of asthma ever and wheeze ever was 11.3% and 19.5% respectively. A study in 1992 reported the respective prevalence rates of 6.6% and 7.8% in schoolchildren of similar age (Leung 1994B). Other epidemiological studies in Hong Kong showed that asthma was present in 7.3 - 10% of schoolchildren between the age of 7 and 15 years (Leung 1994A). However, some of the apparent increases in prevalence may be biased due to the inevitable differences in terms of the study design and questionnaires used. With respect to the study design by comparing two studies on the prevalence of respiratory symptoms in

university students in 1989 and 1994 using the same method, there was a rise in cumulative asthma and current wheeze from 4.8% to 7.2% and 4.6% to 7.6% respectively (Lai 1996A). Therefore, we can conclude that there has been a marked increase in the prevalence of asthma in Hong Kong in recent years.

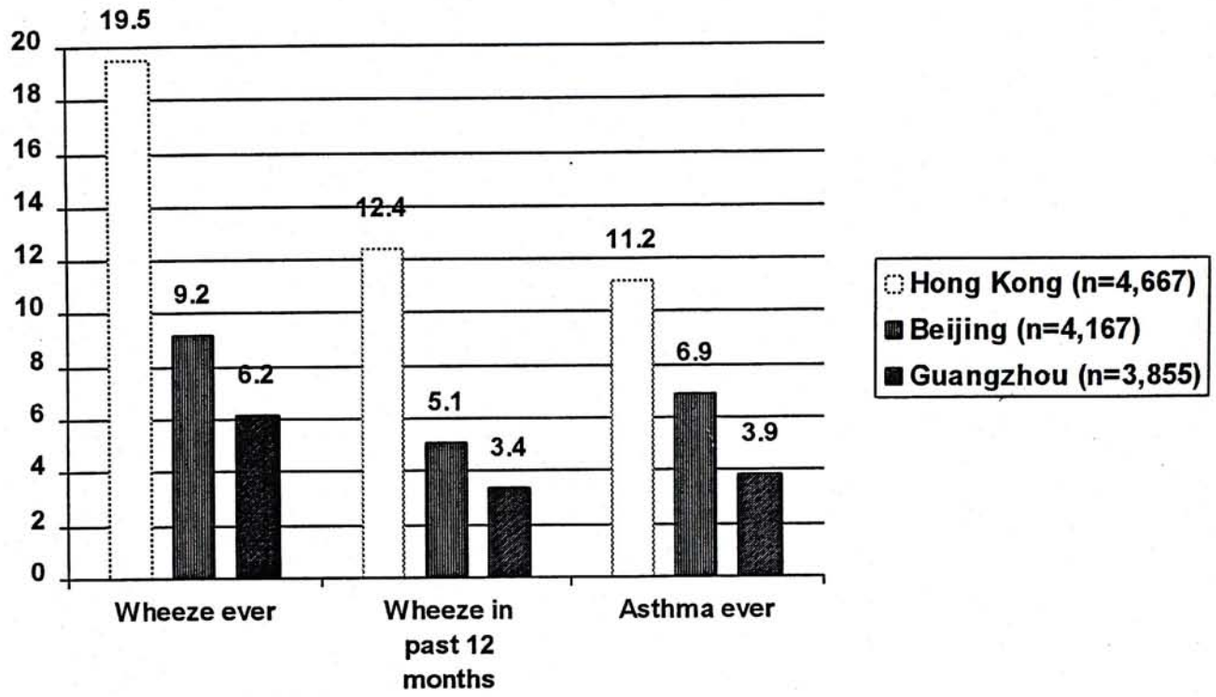
The association of allergic rhinitis and eczema with childhood asthma has been well recognized and is a characteristic feature of the atopic trait. In our study, we used the term itchy rash affecting flexural areas to describe symptoms of eczema without mentioning the name itself. In a previous study in U.K., the sensitivity and specificity of the questionnaire has improved in order to exclude non-atopic forms of eczema and other inflammatory dermatoses (Diepgen 1989). In our study, current rhinitis (OR = 3.07, and 2.90) was associated with current wheezing and severe wheezing attack as well as current eczema (OR = 2.93 and 7.14) by written questionnaire. A previous study revealed that children with a history of eczema at the age of 7 years were more likely to have persistent asthma from early childhood throughout adolescence and into adult life (Jenkins 1994). When the ISAAC data was compared to a previous study on asthma and allergic disease in 1992 (Leung 1994B), the prevalence of asthma ever and wheeze ever in Hong Kong had increased by 71% and 255% respectively (Table 9). Although these two studies used different questionnaires to assess prevalence, another study of university students using identical questionnaire between 1989 and 1994 showed a similar increase on the prevalence rate of asthma ever and current wheeze (Lai 1996A). The rise in asthma prevalence together with other allergic disease over such a short

Table 9. Prevalence (%) of Asthma and Allergic Disease in Schoolchildren in Hong Kong in 1992 and 1995.

	1992 (n=1,062)	1992 (n=1,689)	1995 (n=4,665)
Age range (yrs)	12-16	7-15	13-14
M:F ratio	1.35	1.17	0.99
Asthma ever	6.6 (5.1, 8.1)		11.2 (10.3, 12.1)
Wheeze ever	7.8 (6.2, 9.4)		19.5 (18.3, 20.6)
Wheeze in past 12M	3.7 (2.6, 4.8)		12.4 (11.5, 13.3)
Rhinitis ever	-----		53.1 (51.7, 54.5)
Eczema ever	20.1 (17.7, 22.5)		15.2 (14.2, 16.2)
Sleep disturbance by wheeze in past 12M		3.6 (2.7, 4.5)	4.6 (4.0, 5.2)
Exercise induced wheeze in past 12M		13.0 (11.4, 14.6)	29.1 (27.8, 30.4)
Nocturnal cough in past 12M		11.5 (10.0, 13.0)	27.8 (26.5, 29.1)

period of time is likely to reflect a broadly based change in reactivity possibly due to increased exposure to allergens and other environmental factors.

Figure 2. Comparison of prevalence of asthma symptoms by ISAAC written questionnaire in H.K., Beijing and Guangzhou



The data derived from the ISAAC study by written questionnaire (Figure 2) showed that asthma prevalence was approximately three times higher in Hong Kong when a comparison was made with the data from Guangzhou. With regard to the comparison between Hong Kong and Beijing, asthma was nearly twice as common in Hong Kong than Beijing (Lai 1996B). Although it is a common belief that the extent of pollution in both Guangzhou and Beijing is much worse than that in Hong Kong, the data from the ISAAC study did not support direct impact of air pollution on asthma prevalence at a population level. This particular finding will be clarified in the latter part of the discussion.

The correlation between sex and prevalence of asthma is controversial. The majority of studies indicated that boys are more likely to suffer from asthma than girls (Leung 1994A). The male predominance in prevalence of asthma was also found in the study of secondary schoolchildren aged 13-14 years throughout Republic of Ireland (Manning 1997). In addition, the ISAAC study in Hong Kong showed asthma prevalence to be higher in boys (13.1%) than girls (9.3%). However, ISAAC data from other regions showed that girls are more likely to have wheezing than boys (Pearce 1993). It is noteworthy that a study on asthma and allergy in children has shown no sex difference when the subjects were evaluated by skin prick tests instead of questionnaires (Leung 1994B). With regards to the adult asthmatic group, the atopy rate was found to be 20% higher in males than females (Leung 1997). The causes for the reverse in the gender ratio during adolescence remain unknown. In New Zealand, Sears and his co-workers examined the atopic status in 662 boys and girls at the age of 13 years by skin tests to 11 common allergens. Physician-administered questionnaires were utilized in this study. The information on current and past wheezing, diagnosed asthma, and hay fever were obtained. Sears found that the prevalence of diagnosed asthma increased with increasing numbers of positive response in skin tests, and boys were found to have greater responses to house dust mite (34.0% vs 23.1%) and cat (14.7% vs 11.2%) than girls (Sears 1993). Therefore, gender difference in terms of allergen sensitivity may be partly explained by the gender differences in terms of diagnosed asthma in children.

It was found in our study that children who regularly smoked were more

likely to report recurrent wheezing and severe asthma attack than non-smokers, especially in severe asthma (odds ratio 4.15). Whilst diagnosed asthma and asthma symptoms in smokers was found to increase with age (Paoletti 1989) and atopy and active cigarette smoking have been found to have influences on the recurrence of wheezing during adulthood (Strachan 1996), there is little data on the effect of active smoking on childhood asthma. Although the present data suggests active smoking increase the risk of asthma, a type I error may be possible. Our data might represent a type I error because the actual numbers of active smokers with severe asthmatic attack and current wheeze were small, 14 and 44 respectively. In addition, assessment of smoking status based on self-reporting alone is neither sensitive nor specific. In a study of risk factors for bronchial hyperresponsiveness in children aged 7-16 years, active smoking had no influence on the degree of airway hyperreactivity (Backer 1991). On the other hand, a few studies done by parental reporting were widely implicated in the development of bronchial hyperresponsiveness (Forastiere 1994), development (Martinez 1992) and exacerbation of asthma (Chilmonczyk 1993), as well as recurrent wheezing (Henderson 1995) in susceptible children. In our survey, passive smoking has not been revealed as a significant factor for current asthma and severe asthma attack, which could be partly explained by the unawareness and hence underestimation by the schoolchildren of parental smoking during the most susceptible periods in infancy and early childhood.

The conventional method of studying asthma prevalence is with the use of written questionnaire. However, this may create comprehensive difficulties in some

subjects with different mother tongues. With the video questionnaire, some of these problems can be minimized. It has been shown to be more reproducible than written questionnaire and has equivalent sensitivity and specificity with respect to bronchial hyperresponsiveness (Shaw 1992A). This method should be particularly useful in overcoming language barriers in various populations consisting of different ethnic groups although this has not been widely tested. Our study validated the video questionnaire in assessing asthma prevalence in the oriental population for the first time, and found that it was as good as the written questionnaire in defining asthma symptoms as well as predicting BHR.

When comparing the validity of video questionnaire with that of written questionnaire, BHR was used as the reference in the survey. Generally speaking, in order to estimate the sensitivity and specificity of the challenge test for the diagnosis of asthma in an unselected sample of children and adolescents, bronchial challenge test would be used. In fact, in our study, there were 16 subjects found to have bronchial hyperresponsiveness. Our data also suggested that BHR was quite specific for diagnosing asthma as it was present in 14 of the 16 students (87.5%) who were also labeled with this disease. Furthermore, a life-time diagnosis of asthma was the best predictor for BHR as indicated by its highest Youden's index. Nevertheless, whilst the specificity for either questionnaires in predicting BHR could be increased by including one or more positive responses to the five questions, the associated reduction in sensitivity lowers the corresponding Youden's index (Table 8). Our data as well as others indicated that the audio-visual method was valid for the

estimation of asthma prevalence. In order to minimize any possible bias, the asthmatic symptoms were acted by different ethnic groups in the video questionnaire, e.g. the symptom of "coughing at night" was demonstrated by a Chinese boy from Hong Kong. However, the data revealed that racial impact of these "actors" was probably insignificant as the video sequence with the lowest Youden's index, i.e. coughing at night even though that was played by a Chinese. A similar scene in the Caucasian video questionnaire also has the lowest predictive value for BHR (Shaw 1992A). These results indicated that the interpretation of the video questions is more dependent on the actual symptoms displayed rather than the race of the individual "actor".

According to the result shown in Table 7, the Youden's indices of the four questions except the one on severe wheezing were not significantly different in both questionnaires. The difference between video and written questionnaire versions of the question on "severe wheezing" may be due to the level of comprehension of the definition of severe asthma symptoms by the schoolchildren. It was technically difficult to make the subjects understand the meaning of "severe wheezing". By using the audio-visual aid, schoolchildren could more easily understand the meaning of the questions through the video. On the other hand, video questionnaire may be more useful than written questionnaire in determining the asthma prevalence in developing or the third world countries because of illiteracy and ignorance of asthma symptomatology.

Chapter 4 Environmental survey

4.1 Subjects and methods

4.1.1 SUBJECTS

A total of 40 dwelling-houses were randomly selected from different districts in Hong Kong to participate in the home environment survey. Verbal consent was obtained from one respondent in each household by telephone, and a home visit was arranged. During the home visit, a home survey questionnaire was completed which included information on the type and age of the homes, presence of carpets, pets, smokers and air-conditioners, the types of fuels used for heating and cooking, the type and age of pillows and mattress the respondents used, and the presence of damp patches in the subjects' bedroom. The subjects' homes were visited and surveyed from June to August in 1996. The temperature and relative humidity both inside the homes and outdoor were recorded at the time of the home visits.

4.1.2 QUESTIONNAIRE SURVEY

With regards to the home environmental survey, a written questionnaire was completed in the homes of all subjects. Extra questions concerning the subjects' family members in terms of whether they had asthma, eczema and smoking habits

were also included. The environmental survey was designed to assess important environmental risk factors for asthma and allergies in the subjects' residential surroundings, e.g. the type of housing and the kind of fuel being used for cooking, etc. (appendix 5)

4.1.3 ALLERGENS SAMPLING

Dust samples were collected in the homes of all subjects at the time of home visit. Dust collections were made in four places within the home, namely mattress and bedding, bedroom floor, living room floor and kitchen floor. This was performed in accordance with protocol that were originally developed by Tovey (1981).

A portable vacuum cleaner (Mokita 4071D) was used for collecting all dust samples throughout the study. The dust collecting device consists of several parts: a Motor Unit that holds a nylon bag for storing the dust; an attached tube that keeps the nylon bag in place; a removable oblique wire mesh pre-filter located inside the tube that helps getting rid of the coarse dust since only the fine dust is needed for further analysis.

Sampling:

Samples are obtained from areas which are commonly used by the subjects

during daily activities. Dust samples are collected in order to obtain an objective measure of the concentration of allergen that the subjects have been exposed to at home.

Four specific sites of all subjects' homes have been selected for the collection of dust samples. For each site, a clean nylon bag is used.

Site 1 - Bed: the collection procedure is started by vacuum cleaning the mattress, particularly the areas that have been used by the subjects during sleep. In addition, pillows, pillow cases, duvets and sheets are also included in the process. The total area sampled is about 1 square meter and the total collecting time is one minute.

Site 2 - Bedroom Floor: the selected areas being vacuumed are places where dust can be abundantly found. As for a room which is fully carpeted, an area of approximately one square meter is vacuumed for one minute. In the case of an uncarpeted room, a total area of two square meters of the bedroom floor is vacuumed. Specific zones of the bedroom floor such as the areas next to the bed as well as that towards the center of the bedroom are particularly important and are included in the dust collection.

Site 3 - Living room: When sampling from carpets (or any combination of carpets, rugs, mats or uncovered surfaces), an one square metered area is selected either from the center of the room or that near to any soft furnishings. The total vacuum cleaning duration for both cases is one minute. With respect to the sampling from a totally uncarpeted surface, collection was done on a two square metered hard floor for one minute.

Site 4 - Kitchen floor: similar method was applied on the collection from the kitchen floor as for the living room.

Each of the nylon bags containing the collected dust samples is placed in a transparent plastic bag. In addition, each individual bag is clearly labeled with the subject's name, a code, the date of collection and the specific site of dust sampling. All sealed plastic bags were stored in refrigerators at the temperature of -20 °C before allergen assays.

Dust samples were assayed for major allergens of dust mite (Der p 1), cat (Fel d 1), and cockroach (Bla g 2) by monoclonal antibodies assay according to published protocol (Pollart 1991). The analysis were performed at the Department of Chemical Pathology of the Chinese University of Hong Kong.

Tube sampler for NO_2 (Nitrogen dioxide)

The NO_2 samplers are acrylic tubes containing a stainless steel mesh disk coated with triethanolamine at one end, which serves to absorb NO_2 in the air. At the other end of the tube is a colourless polythene cap which is removed at the beginning of NO_2 collection, leaving the sampling tube in contact with atmospheric air during the collection period.

In each home, 3 NO_2 sampler tubes are affixed vertically on suitable surfaces in the bedroom, living room and kitchen with adhesive tape. The exposure period for each group of tubes ranged from one to two weeks. As for the positioning of the tubes, the opening of the tube is placed facing down. In addition, the time and the date at which the collection process started and ceased are clearly noted on the labels; hence, the total exposure time can then be calculated. The tubes are recapped at the end of the sampling.

The stationary NO_2 samplers are collected at the end of the collection period during the second home visit. They are stored in the refrigerator at 0-4 °C. All the NO_2 samplers are then sent to the Environmental Protection Department of Hong Kong in batches for analysis.

4.2 Result-environmental survey

Table 10 showed the characteristics of 40 dwelling-houses studied in Hong Kong. The mean years of residence was 7.6 +/- 4.8. Over 90% of the surveyed homes were apartments that were either privately owned or pubic housing estates. These homes were located on first to 40th floor of the building. About half of the homes had two bedrooms excluding bathrooms and kitchen. In addition, 10 families had 3 bedrooms and 9 families had just one bedroom. The majority of subjects used synthetic pillows but there were 9 subjects whose pillows comprised both synthetics and feather. Mould patches and dampness were commonly found on the bedroom walls, with 11 of the 40 homes (27.5%) were found to have both. With the exception of one family using electrical cooking appliance, all other subjects used gas as their main fuel for cooking (97.5%). More than half of the families did not possess heating utilities in the apartments but there were 18 homes using electricity for heating purpose. Although current pet ownership was found to be low at 2.5%, 10% of the homes visited had removed pets in the past due to complaints made by one or more members in the household in terms of allergic symptoms. Similarly, 5 of the 40 homes had re-arrangements in the bedroom in order to avoid allergies.

Table 11 showed the distribution of the 3 indoor aeroallergens surveyed namely Der p 1, Fel d 1 and Bla g 2. All 3 inhalant allergens assayed were widely distributed within the homes with 85% of dust samples from the 4 sites contained detectable levels of 1 or more of the 3 allergens. In particular, Der p 1 was present in all the dust samples collected from the mattress and the bedroom floor. More

importantly, over 50% of samples from these 2 sites contained levels of Der p 1 ≥2μg/g, the proposed threshold for mite sensitization to develop. Der p 1 levels were higher in mattress samples than the other 3 sites ($p<0.05$). On the other hand, although Fel d 1 was also readily detectable in the majority of samples from all niches, the levels were low and did not exceed the critical level of 8μg/g of dust in any of the samples. The cockroach allergen, Bla g 2, was present in low levels ranging from 0.1-0.6 units/g of dust, with the highest level found in the kitchen. All of the 40 homes contained detectable levels of all 3 allergens in at least 1 site within the homes.

Table 12 shows the distribution of indoor NO_2 and the data were collected by using stationary tubes which had been placed in the homes for a period of time. Within each study home, the tubes were placed in the bedrooms, lounges and kitchens. NO_2 concentration was detected in all 40 samples homes. The lowest concentration of NO_2 was 6.5 ppb in one sample which was collected in the lounge room. Meanwhile, the highest NO_2 level was recorded in the kitchen reaching 157.9 ppb in one apartment. In general, the NO_2 levels were higher in the kitchens than the bedrooms and lounges which had similar levels, but the difference did not reach statistical significance.

Table 10 Characteristics of 40 residential homes in Hong Kong

		%
Years of inhabitation (mean±s.d.)	7.6±4.8	
Number of bedrooms		
1	9	22.5
2	20	50.0
3	10	25.0
4	1	2.5
Pet ownership		
Cat	1	2.5
Dog	1	2.5
Bird	1	2.5
Types of pillow		
Synthetic	28	72.5
Feather	1	2.5
Both	9	22.5
Types of quilt		
Synthetic	29	75.0
Feather	0	0
Unspecified	10	25.0
Age of mattress (mean, in years)	4.1±2.9	
Visible patches of dampness on bedroom walls	11	27.5
Visible patches of mould growth on bedroom walls	11	27.5
Removal of pets because of allergy in family members	4	10.0
Alteration in bedroom because of allergy	5	12.5
Types of fuels used for cooking		
Gas	39	97.5
Electricity	1	2.5
Types of fuels used for heating		
No home heating	22	55.0
Electricity	18	45.0
Presence of smokers	10	25.0

Table 11 Distribution of common indoor allergens in residential homes in Hong Kong

Sites	Der p 1					Fel d 1					Bla g 2			
	%		μg/g			%		μg/g			%	units/g		
	+ve	>2μg	AM	GM	Max	+ve	>8μg	AM	GM	Max	+ve	AM	GM	Max
Mattress	100	80	22.9	8.83	157.8	87.5	0	0.3	0.06	3.7	92.5	0.1	0.09	1.1
Bedroom floor	100	50	2.5	1.59	7.9	95	0	0.3	0.08	2.7	90	0.2	0.14	1.4
Lounge room	92.5	35	2.0	1.27	11.0	90	0	0.4	0.09	7.6	92.5	0.3	0.16	1.0
Kitchen	90	20	1.6	0.74	19.5	85	0	0.2	0.06	4.2	92.5	0.6	0.20	9.1

(AM: Arithmetic Mean; GM: Geometric Mean)

Table 12 Distribution of indoor NO_2 in residential homes in Hong Kong

Sites	NO_2			
	+ve (%)	Min (ppb)	Mean (ppb)	Max (ppb)
Bedroom	100	10.1	30.9	69.1
Lounge room	100	6.5	31.7	73.7
Kitchen	100	20.5	48.7	157.9

4.3 Discussion-environmental survey

The aim of the home survey is to investigate risk factors within the home which may be important for studying asthma and allergies in Hong Kong. The home visits were performed between June and August, 1996, i.e. the summer months in Hong Kong. Within this period when the survey was done, the average temperature and relative humidity exceeded 26°C and 80% respectively on most of the days.

The major mite allergen (Der p 1) was found to be present in all the dust samples from the bedding and the bedroom floor of the homes. In addition, half of these dust samples contained levels of Der p 1 exceeding 2 μg Der p 1 per gram of dust, the threshold for mite sensitization (Platts-mills 1989). When our findings were compared with another study in Hong Kong in 1982 (Gabriel 1982), the difference between the mean density values of Der p 1 in the dust samples collected from the bedding were founded to be distinct. In 1982, the mean level of dust mite in bedding of asthmatic patients was 833 mites per gram of dust, equivalent to 16.7 μg of Der p 1 per gram of dust (Platts-Mills 1989), and the maximum level was 52.7 μg/g. Therefore, it can be concluded that the present level of Der p 1 is very high (Arithmetic mean: 22.9, Max.: 157.8). However, the extremity may be explained by difference in assessment of mite exposure; a brushing kit was used in the 1982 study for the collection of dust samples instead of vacuum cleaner, and mite count was used as the standard for mite exposure whilst concentration of Der p 1 was used in

the current study. However, it is clear from both studies that mite allergen is ubiquitously present in Hong Kong and may be an important trigger for asthma.

According to other mite allergens studies from many different countries, the levels of mite allergen in residential homes vary greatly. In the coastal region of Sydney, Australia, a study on 1339 schoolchildren aged 8-11 years showed that the mean (geometric) level of Der p 1 was 22.5 μg/gm. This value was about three times higher than our data of 8.8 μg/gm. Furthermore, the prevalence of current wheezing has been found by written questionnaire to be 23.9% in the Australian population, which was twice as high as that of Hong Kong , i.e. 12.4% (chapter 3). It is therefore possible that one of the factors accounting for the difference in the prevalence of asthma between the two regions could be determined by the levels of mite allergens within homes. On the other hand, studies from other South-East Asian countries gave different results. For instance, in Singapore, the prevalence of asthma in children was 12.3% which was similar to that of the Hong Kong study. However, the Der p 1 levels in the mattress dust in the Singaporean residential homes were much lower at 1.2 μg/gm (Zhang 1997). In this study, up to 97% of the dust samples from mattress contained allergens of *Blomia tropicalis*, a glycolipid mite. In the tropical and subtropical geographic regions including Hong Kong, *B.tropicalis* has been found in large number in the dust samples collected from homes (Gebriel 1982, Arlian 1993), and in tropical areas it may even be regarded as an important source of allergens in the house dust rather than other mites (Caraballo 1994). Since there is no available assay of *B.tropicalis* allergen in Hong Kong, the

concentration of *B.tropicalis* in the dust samples collected for the Hong Kong study is unknown.

It has been reported in several countries that cat-derived antigen represents the second most important source of indoor allergens after house dust mites (Warner 1992), and in some areas it may even be the predominant sensitizer (Munir 1993). Pet ownership was found to be low in Hong Kong. There were 4 households in our sruvey, which removed domestic pets to reduce allergic complaints. In general, domestic pet ownership is higher in temperate climate reaching 50% in some countries (Bollinger 1996) than in tropical and subtropical populations (Zhang 1997). Although there was only one subject found to own cat at home in our study, it was interesting to find that more than 85% of the dust samples collected from the homes in Hong Kong contained the major cat allergens, Fel d 1. It was widely present in living rooms, bedrooms, as well as kitchens. Indirect contacts with cat allergen by the subjects from upholstered seats in public buildings and public transport (Custovic 1994), and clothing of people who have regular exposure to cats (Enberg 1993), can lead to significant exposure and may be clinically relevant. Compared with the arbitrary cutoff level of Fel d 1 of 8 μg/g dust (geometric mean), the proposed risk level for acute asthmatic exacerbations in cat-sensitive patients (Gelber 1993), none of the dust samples in our study exceeded this level. However, recent studies suggested that sensitization to indoor allergens could occur at a lower level (Munir 1993, Wickman 1991) and that doses lower than those causing bronchoconstriction could cause increase in nonspecific bronchial

hyperresponsiveness (Ihre 1988). It has been suggested that a concentration of 1 μg/gram Fel d 1 of dust, or less, may be sufficiently high to cause perennial symptoms in cat-sensitive asthmatic patients (Munir 1993).

We found that more than 90% of dust samples were positive to Bla g 2, the major species-specific allergen of *B.germanica* but its level was very low when compared with a survey in southeastern San Diego, United States where a mean value of 7.13 U/gm dust was found (Christiansen 1996). According to our results, kitchens had the highest concentration of allergens in home and this may be due to the fact that foods stored in kitchen become a major source of food for cockroach. By using extracts containing allergens derived from a mixture of different cockroach species, positive skin tests were found in 25.7% of the schoolchildren (Leung 1994B) and in 40.7% of adults with asthma (Leung 1997). To explain the difference between high level of sensitization to cockroach and low concentration of cockroach allergen within homes, it is possible that the German cockroach is not the major species that cause sensitisation. Indeed, there was evidence to suggest that the American cockroach (*Periplaneta americana*) is the predominant species in South-East Asia (CH Wu, personal communication). In addition, over 65% of 250 subjects with acute asthma admitted to a teaching hospital in Hong Kong showed that they contained specific IgE to the allergens of *P. americana* in the sera. A European study showed that *Blattella Orientalis* accounted for most of the cockroach sensitization in a group of patients with rhinitis and asthma, living in an urban area. They were assessed by skin test and measurement of serum specific IgE antibody to

cockroach extracts (Sastre 1996). In another study, cross-reactivity was found to exist between shrimp, an important food allergen, and German cockroach (Crespo 1995). It is therefore essential to determine the clinical significance of cross-allergy to both allergens and their relative exposure in future studies in Hong Kong.

Nitrogen dioxide is a common indoor pollutant which is mainly emitted from gas cooking and kerosene space heaters (Samet 1991). In most of the families in Hong Kong, natural gas stoves are more commonly used as the main cooking appliance rather than electrical stoves. However, the exposure to natural gas stoves has been associated with the prevalence of asthma, wheezing in the preceding 12 months and hay fever in one study (Volkmer 1995). In our study, the highest level of NO_2 in a "kitchen sample" was found to be 157.9 ppb. The data indicated that the NO_2 levels in the kitchens were about 1.5 times higher than that recorded in the bedrooms and lounge rooms. This phenomenon was likely to be caused by gas cooking with poor ventilation in the kitchen area. It is known that exposure to 400-800 ppb of NO_2 can cause bronchial epithelial cell dysfunction in an in-vitro study by Devalia *et al.* (1993). By using personal NO_2 samplers, a previous study in Hong Kong showed that the average level of exposure to NO_2 over a 24-hour period was about 18-20 ppb, and higher levels were detected in those who were exposed to stoves powered by piped gas but not kerosene (Koo 1990).

Although inhalation of NO_2 has been found to cause inflammatory influx into the airways of healthy individuals (Sandstrom 1991), there is no data on the health

effects of acute inhalation of NO_2 and other pollutants at concentrations found during episodes of pollution. With respect to the NO_2 level in the kitchen during cooking with a gas stove, concentrations of nitrogen dioxide may reach 400 ppb in a short periods, 10 times higher than average outdoor concentration of 40 ppb. According to a previous study, subjects living in more modernized and developed country were found to spend about 90% of their time indoors (Quackenboss 1982). In addition, another study suggested that NO_2 at concentrations encountered in the home environment can potentiate specific airway response in patients with mite-sensitive asthma (Tunnicliffe 1994). The use of gas cooking has been found to be significantly associated with respiratory morbidity in women but not in men (Jarvis 1996). Women may be more susceptible to the products of gas combustion than men because they may have greater exposure to high concentrations of these by-products due to a longer time of exposure in the kitchen.

With regard to the effect of NO_2 on airways responsiveness, it was found that bronchial responsiveness to histamine was more significant at 5 hours following NO_2 exposure when compared with that of the exposure to air (Strand 1996). These results suggested that exposure to an ambient level of NO_2 may have delayed effect on bronchial responsiveness in asthmatics. This is also compatible with the enhancement of airway inflammation even if the lung function parameters and cellular composition of bronchoalveolar lavage fluid have not been proved to be markedly affected (Jorres 1995). The relationships between visits to the emergency room due to asthma attacks and the meteorological, aerobiological, and chemical

characteristics of the outdoor air have been evaluated. Increased levels of pollutants, especially NO_2, were found to be associated with attacks of asthma (Rossi 1993).

In conclusion, although a few studies shown that air pollutants such as particulate matters and SO_2 are important triggers for asthma attack in those who have already had the disease, there is no evidence that they are important risk factors in the development of asthma or implicated in the increasing prevalence of asthma. In a carefully conducted study compared respiratory symptoms and allergy in population samples of children living in a Poland with that of children living in less polluted and more affluent rural and urban regions of Sweden (Braback 1994), cough and breathlessness were three times more common in the Polish children, but fewer were sensitized to common allergens. Moreover, surveys in the developed world have shown that more affluent sections of the community have the highest prevalence of allergic sensitization and asthma. Of considerable interest have been the recently reported findings of the prevalence of bronchitis and allergic diseases in the former East and West Germany. While bronchitis is much more common in former East Germany with high levels of industrial pollutants, asthma, hay fever, and allergic sensetization assessed by skin testing were up to threefold more frequent in West Germany with more affluent living standards (von Mutius 1994). The environmental factors which are responsible for the differences in asthma prevalence remain speculative. However, recurrent infections early in life may have a protective effect against the development of allergic disorders including asthma. The hypothesis is that viral infections may favour the differentiation of T helper (TH)

cells to the TH_1 phenotypes. TH_1 cells, with the release of the cytokine IFN-Y, inhibit IgE synthesis which is a key feature in atopic asthma and thereby reduce the likelihood of developing allergies (Martinez 1994).

In our study, the distribution of some important indoor allergens such as house dust mite, cat allergen, cockroach allergen and NO_2 were analyzed. The data obtained may be useful for comparison with those from other places where asthma prevalences may be significantly different from ours. Such comparisons may suggest of these allergens and pollutant may be important causative factors for asthma.

Chapter 5. Overall discussion and conclusions:

There is considerable concern that the prevalence and severity of asthma is rising all over the world. The possibility of increasing prevalence is difficult to access because of the lack of the clear-cut definition of asthma and the difference in methodology in the epidemiological studies. Using identical methodologies, ISAAC was established in order to describe the prevalence and severity of asthma, allergies rhinitis and eczema in the children living in different areas.

In comparison with the previous studies in Hong Kong, data from the ISAAC written questionnaire supports the view that the prevalence of asthma and other allergic symptoms has increased over the recent years. Compared with data from other ISAAC centers, the prevalence of asthma in schoolchildren living in Hong Kong was nearly twice as common as that in Beijing, and was three times higher than that in Guangzhou.

A sample of schoolchildren was selected to undergo BHR testing and complete the video questionnaire, which comprise of the audio-visual presentation of clinical signs and symptoms of asthma. It was confirmed that video questionnaire is more reproducible than written questionnaire and has equivalent sensitivity and specificity for BHR as determined by inhaled methacholine. Thus it is a valid and

reliable method for determining asthma prevalence. It is preferred particularly in the study populations with different cultures and languages.

With respect to genetic background, temperature, relative humidity and life style, schoolchildren in Hong Kong and Guangzhou share a number of similarities, but the prevalence of asthma was higher in the former than the latter by both questionnaires in ISAAC. The data suggested an important role of environment factors on the pathogenesis of asthma. The role of inhalant allergen and indoor air pollution were explored in the thesis.

In the environmental study, the concentration of three inhalant allergens, namely the major mite allergen (Der p 1), the major cat allergen (Fel d 1) and one of the major cockroach allergens (Bla g 2) in dwelling-houses were determined. Mite allergen is the most common inhalant allergen and was found to be widely distributed in these homes. Der p 1, Fel d 1 and Bla g 2 were ubiquitously present but levels were generally low except for Der p 1 which frequently exceeds the threshold for sensitization. Other allergens such as cat and cockroach are also important although they were not found in similar distribution as mite. In addition, NO_2 distribution in dwelling-houses in Hong Kong was defined. The level of exposure to NO_2 has increased compared to previous data. Although there was little difference in NO_2 concentration between 3 collection sites in the homes, the highest concentration was recorded in the kitchen. This will form the basis for future

aetiological study into the relative role of NO_2 exposure in the pathogenesis of asthma and allergic disease.

In short, the prevalence of asthma in Hong Kong has been confirmed to have increased compared to data obtained from previous studies. Both written questionnaire and video questionnaire indicated that the prevalence of asthma and current wheeze were about four times higher in Hong Kong than that in Guangzhou. By the use of identical study methods in ISAAC, these variations are likely to be genuine rather than an artifact as a result of methodology difference. Indoor environmental factors can partly explain the rapid increase in the prevalence of asthma and allergic disease in Hong Kong.

Future direction:

The results conducted from ISAAC Phase I and home survey in this thesis have provided information on the trend in prevalence and severity of asthma and allergies and determined the distribution of the common inhalant allergens and NO_2 in dwelling-houses in Hong Kong. These findings will be used in future studies to compare indoor environment between populations with contrasting asthma prevalence and to determine the time trend of asthma prevalence and morbidity in the territory.

The Phase II of ISAAC will be performed in 1997-1998 which aims to assess differences between populations with a different focus in terms of asthma prevalence, indoor environment, lifestyle and medical care. It is envisaged that in ISAAC Phase II, the pathogenic role of the environment can be objectively studied and individual factors carefully assessed to provide valuable information which may explain the global distribution and increasing trend of asthma and allergies today.

Hong Kong, a western international city with a majority of oriental people, has a relatively high prevalence of asthma in the Far East. By using the valid and reproducible method like video questionnaire, data from different places can be compared to avoid experimental error. The home survey provided baseline data on characteristics of home environments and the preliminary data of some important indoor allergens distribution in Hong Kong. Carefully planned investigations using standardized methodologies, like those of ISAAC, will provide valuable information not only on the health cost of asthma but also on its aetiology.

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健康問題調查問卷

請回答以下問題：

今天日期或填寫問卷日期：　□ 日　□ 月　□ 年

姓名：

就讀學校：

就讀班級：

年齡：　□ 歲

出生日期：　□ 日　□ 月　□ 年

請回答以下問題，并在適當的答案空格內填上（√）。
如果選擇錯誤，請劃去原先答案，并在適當的答案空格內填上。

你是：　□ 男性　□ 女性

你是：　□ 華人　□ 非華人

請註明：

(以下問題，請在適當的答案空格上加上「√」號)

性別：　□ 男　□ 女

1. 你的胸部過往有沒有曾經發出喘聲，氣緊或 He He 聲？
【若你的答案是「沒有」，請跳往問題 (6)】
□ 有　□ 沒有

2. 過去12個月內，你的胸部有沒有發生喘聲或 He He 聲？
【若你的答案是「沒有」，請跳往問題 (6)】
□ 有　□ 沒有

3. 平均來說，過去12個月內，你曾有過多少次氣緊？
□ 沒有　□ 一至三次　□ 四至十二次　□ 十二次以上

4. 平均來說，過去12個月內，你約有多少次是因爲這些氣緊而不能入睡?
□ 從沒有　□ 每星期少於一晚　□ 每星期一或多晚

5. 過去12個月內，你有沒有因爲氣喘到太嚴重而影響說話能力，每次吸氣只能講一至兩個字？
□ 有　□ 沒有

6. 你過往有沒有曾經患上哮喘？
□ 有　□ 沒有

7. 過去12個月內，你運動的時候或運動之後，胸部有沒有發生喘聲？ □ 有 □ 沒有

8. 過去12個月內，除了患上傷風或肺部受感染之外，你晚上有沒有乾咳？ □ 有 □ 沒有

問題 9-15 是指一般健康情況，若患上傷風或感冒均不適用

9. 你有沒有曾經患有打噴嚏，流鼻水或鼻塞問題？（注意：傷風或感冒的時候不計算在內）【若你的答案是「沒有」，請跳往問題（14）】 □ 有 □ 沒有

10. 過去12個月內，你有沒有患有打噴嚏，流鼻水或鼻塞問題？（注意：傷風或感冒的時候不計算在內）【若你的答案是「沒有」，請跳往問題（14）】 □ 有 □ 沒有

11. 過去12個月內，除了鼻部不適外，你有沒有流眼水和眼睛痕癢的問題？ □ 有 □ 沒有

12. 過去12個月內，上列鼻部不適在那些月份出現？

（請在適當的月份加上「√」號）

☐ 一月　☐ 二月　☐ 三月　☐ 四月

☐ 五月　☐ 六月　☐ 七月　☐ 八月

☐ 九月　☐ 十月　☐ 十一月　☐ 十二月

13. 過去12個月內，上列鼻部不適怎樣影響你的日常生活？

☐ 毫無影響　☐ 些微影響　☐ 相當影響　☐ 嚴重影響

14. 你有沒有曾經患上花粉熱？

☐ 有　☐ 沒有

15. 你有沒有曾經患上鼻敏感？

☐ 有　☐ 沒有

16. 你有沒有一些痕疹持續半年或以上都未消散？

☐ 有　☐ 沒有

【若你的答案是「沒有」，請跳往問題（21）】

17. 過去12個月內，這種痕疹有沒有發作？

☐ 有　☐ 沒有

【若你的答案是「沒有」，請跳往問題（21）】

18. 這種痕疹有沒有影響以下身體部位：

手肘內側，膝頭後面，腳踝前面，臀部下端，頸、耳朵

☐ 有　☐ 沒有

19. 過去12個月內，這種痕疹有沒有完全消散？ ☐ 有 ☐ 沒有

20. 過去12個月內，你平均有多少時候是因爲這種痕疹而不能入睡？ ☐ 過去12個月內從無影響 ☐ 每星期少於一晚 ☐ 每星期多於一晚

21. 你過往有沒有曾經患上濕疹？ ☐ 有 ☐ 沒有

22. 你的父親的教育程度是：
初中 ☐ 高中 ☐ 大專程度 ☐

23. 你的母親的教育程度是：
初中 ☐ 高中 ☐ 大專程度 ☐

24. 你的家裏有沒有人吸煙：
有 ☐ 沒有 ☐

如果是有的話，吸煙的人是誰：（你可以選擇多個答案）
父親 ☐ 母親 ☐ 其他人 ☐ _____
（請註明）

25. 你曾否吸煙：

有 ☐ 沒有 ☐

如果是有的話，你現在吸煙的次數是：

至少平均每日一次 ☐

少過一日一次，但至少每星期一次 ☐

少過一星期一次 ☐

我現在不吸煙 ☐

26. 你家裏有沒有冷氣機：

有 ☐ 沒有 ☐

如果是有的話，是安裝在：（你可以選擇多個答案）

客廳 ☐ 你的睡房 ☐

錄影帶問卷

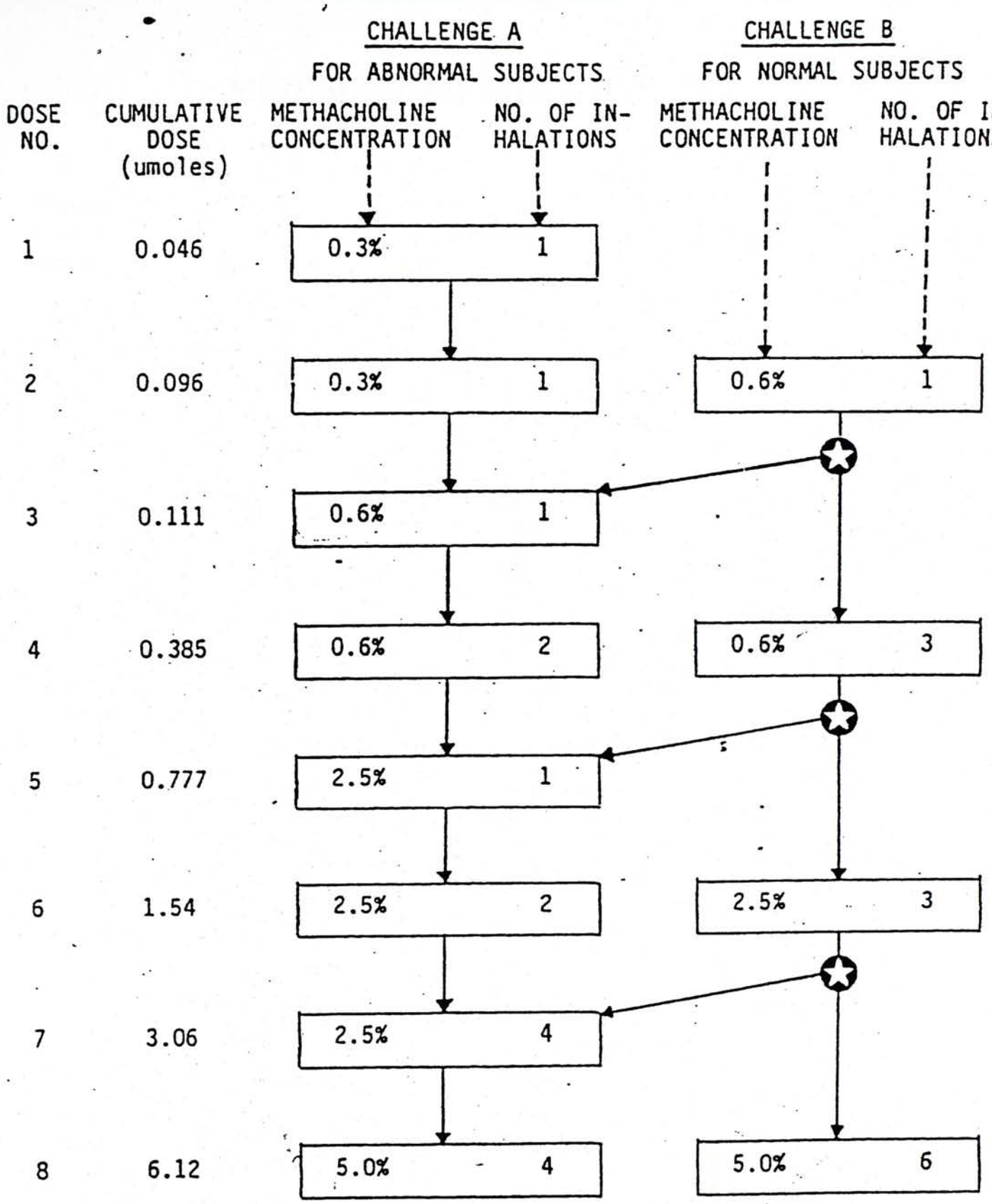
姓名 _____ _____ 年齡 _____

性別 _____ 出生日期 _____

學校 _____ 聯絡電話 _____

	是	否
一) 你在一生中，曾否出現過像片斷中的這種呼吸狀態？	☐	☐
若有： 在去年出現過？	☐	☐
若有： 每月出現一次或多次？	☐	☐
若有： 每週出現一次或多次？	☐	☐
二) 你在一生中，曾否發生過像片斷中穿深色衣服的男孩那樣在運動後這種呼吸狀態？	☐	☐
若有： 在去年出現過？	☐	☐
若有： 每月出現一次或多次？	☐	☐
若有： 每週出現一次或多次？	☐	☐
三) 你在一生中，曾否發生過像片斷中那樣在夜間喘醒？	☐	☐
若有： 在去年出現過？	☐	☐
若有： 每月出現一次或多次？	☐	☐
若有： 每週出現一次或多次？	☐	☐
四) 你在--生中，曾否發生過像片斷中那樣在夜間咳醒？	☐	☐
若有： 在去年出現過？	☐	☐
若有： 每月出現一次或多次？	☐	☐
若有： 每週出現一次或多次？	☐	☐
五) 你在一生中，曾否發生過像片斷中的呼吸狀態？	☐	☐
若有： 在去年出現過？	☐	☐
若有： 每月出現一次或多次？	☐	☐
若有： 每週出現一次或多次？	☐	☐

CHART OF METHACHOLINE DOSES



STOP CHALLENGE WHEN FEV_1 FALLS BY MORE THAN 20%

✪ If change in FEV_1 > 10% and < 20%, go to Challenge A

If Change in FEV_1 < 10%, continue with Challenge B.

METHACHOLINE CHALLENGE TEST

Name: Sex/Age: I.D.no:

Date: Height: Weight:

Concentration	No. of inhalation	FEV_1 recorded 1min after inhalation (L)	FEV_1 % fall
Pre.			
N.S.	1		
0.3%	**1**		
	1		
0.6%	1		
	1		
	2		
	3		
2.5%	1		
	2		
	3		
	4		
5%	4		
	6		
Post B.D.			

Precondition

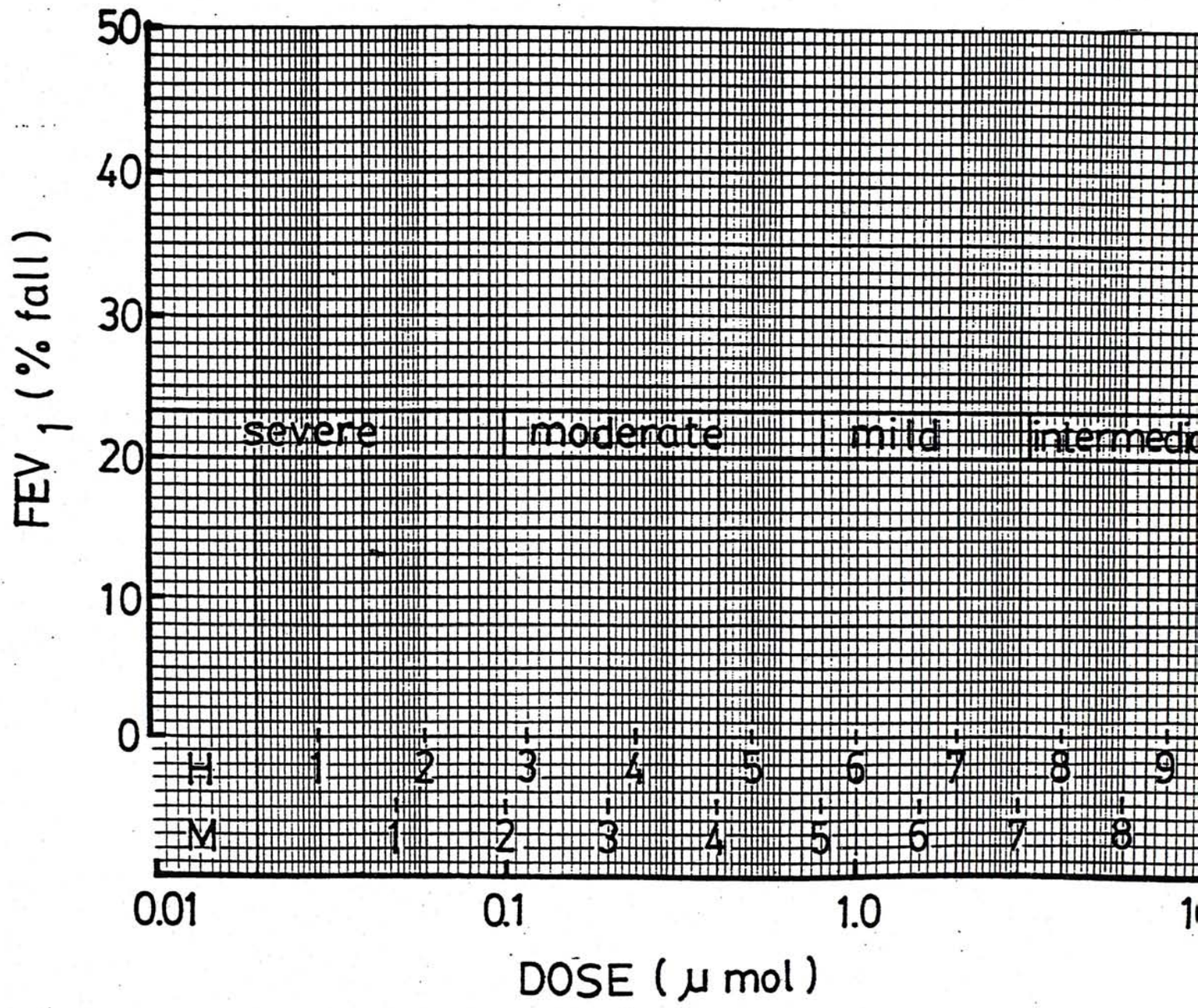
1. $FEV_1/FVC > 50\%$;
2. Exclude $FEV_1 < 60\%$ predicted;
3. Stop challenge when FEV_1 falls by more than 20%.

BRONCHIAL CHALLENGE TEST
RESPIRATORY UNIT, PRINCE OF WALES HOSPITAL

NAME: SEX/AGE:

I.D. NO.: UNIT/WARD:

DIAGNOSIS: DATE OF TEST:



$PD_{20}FEV_1$ _____ μmol $PD_{20}PEFR$ _____ μmol

	FEV_1	FVC	FEV_1/VC	PEFR
Predicted				
Initial (% pred)				
Post B/D (% pred)				

COMMENT:

HOME ENVIRONMENT SURVEY

1. What area do you live in? _____ Floor_____

2. What type of housing do you live in?

*Private housing_____

Housing estate_____

Others_____

3. For how many years have you lived in your present house?

_____years

4. How many rooms are there in your home, excluding kitchens and bathrooms?

_____rooms

5. Do you keep any household pets at the time when you were born?

*Yes_____No_____

If YES, do you keep any of these pets: (tick as many as apply)

*Dog_____

Cat_____

Other furry pets_____

Bird_____

6. Did you keep any household pets at the time when you were born?

*Yes_____No_____

If YES, do you keep any of these pets: (tick as many as apply)

*Dog_____

Cat_____

Other furry pets_____

Bird_____

7. Have you ever got rid of a pet or decided not to have one because you thought that one of the family might be allergic to it?

*Yes_____No_____

8. What kind of pillow do you use?

*Synthetic_____

Feather_____

Both_____

Other_____

9. What kind of eiderdown or continental quilt do you use?

*Synthetic_____

Feather_____

Both_____

Other_____

10. How old is the mattress on your bed?

_____years

11. Are there damp patches on the walls of your bedroom during the winter months?

*Yes_____No_____

12. Are there patches of fungus or mould growth in your bedroom at any time of years?

*Yes_____No_____

13. Have you made any alterations or special arrangements in your bedroom because of allergy, asthma or other chest problems?

*Yes_____No_____

14. Which fuel do you use for cooking on the hob or rings?

*Gas (e.g. mains gas, bottled gas)_____

Electricity_____

Other (please specify)_____

15. Which fuel(s) are used for heating your home?

*Electricity_____

Mains gas_____

Bottled gas_____

16. When you were born, which fuel did you use for cooking on the hob or rings at that time?

*Gas_____

Electricity_____

Other (please specify)_____

Can't remember_____

17. When you were born, which fuel(s) was used for heating your home at that time?

*Electricity_____

Mains gas_____

Bottled gas_____

Can't remember_____

18. Has your mother ever had the following symptom(s)?

a) Wheezing or whistling in the chest *Yes_____No_____

b) Asthma Yes_____No_____

c) Hay fever Yes_____No_____

d) Eczema Yes_____No_____

19. Did she smoke cigarettes during pregnancy while she was expecting you in our survey?

*Yes_____No_____Not natural mother_____

If YES, how many cigarettes did she smoke each day, on average, at that time?

_____per day

20. Has your father ever had the following symptom(s)?

a) Wheezing or whistling in the chest *Yes_____No_____

b) Asthma Yes_____No_____

c) Hay fever Yes_____No_____

d) Eczema Yes_____No_____

21. Did he smoke cigarettes around the time when you were born?

*Yes_____No_____

Not natural father_____Don't know_____

22. Are you exposed to passive smoking?

*Yes_____No_____

If YES, 1) Where are you exposed to passive smoking?

*Work_____Home_____Both_____

2) How frequency are you exposed to passive smoking?

*Daily_____Three times a week_____weekly_____

*please give a ___✓___ to the appropriate answer